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Clinical Evaluation and Management of Tumors of the Breast*

GERSON J. LESNICK, M.D.

Introduction

The breasts are superficial organs and readily accessible. They can be seen and felt easily. Therefore, it is not surprising that 90% of breast tumors can be delineated by physical examination. Seventy-five percent to 80% of breast tumors are discovered by patients, another 15% by physicians in the course of physical examinations, and only 5% to 10% are first discovered by mammographic screening.

Properly performed physical examination of the breasts is very accurate in determining the nature of a breast tumor. Features noted on physical examination are also the basis for clinical staging of the extent of the disease.

Examination begins with a detailed history in which, in addition to the description of the patient's complaints in relation to the breast, historical data relating to risk of breast cancer should be elicited. Specifically these are the patient's age, family history of breast cancer, nulligravidy or first parity after age 34, previous breast cancer in the opposite breast, and previous exposure of the breast to ionizing radiation. Previous surgical procedures on the breast should be noted. There may have been earlier lesions associated with a higher risk of breast cancer, such as lobular neoplasia or intraductal papillomatosis. Knowledge of previous breast surgery is also important in evaluating breast deformities and evident skin retraction, as these may be merely secondary to scarring from an earlier operation.

Technique of Examination

The breasts should be examined first with the patient sitting. In this position, the supraclavicular fossae and axillae are palpated carefully for evidence of adenopathy at either site. The breasts should be inspected both with the patient's arms at her sides and with her arms raised over her head. The latter may bring out skin retraction that was not noticeable when her arms were at her sides. Another maneuver that may demonstrate adherence of the tumor to the overlying skin is to have the patient place her hands on her hips and then contract the pectoral muscles by trying to press her hands together. She may also lean forward, resting her weight on her hands, which are supported by the examiner. Using all of these maneuvers may uncover evidence of adherence of the tumor to the overlying skin. (Such adherence, when it is not due to scarring from a previous operative procedure, almost always indicates that the tumor responsible for it is malignant.) The patient then lies down for the remainder of the examination.

Palpation of the breast should be thorough and methodical. Examination should follow some pattern that covers the entire breast. Segments of the breast may be examined in a transverse pattern or in a radial pattern. All breast tissue must be palpated. It should be remembered that breast tissue exists in the subcutaneous tissue from the level of the clavicle to a point about 2 to 3 cm below the inframammary fold, and from the sternum laterally to the lateral edge of the latissimus dorsi muscle. Often palpation is facilitated if the patient lifts her arm up and places it alongside her head. The examination should be performed by feeling the breast substance against the chest wall using the flat portion of the middle three fingers.When breast tissue is picked up and examined between thumb and fingers, spurious tumors may be felt and actual tumors may be missed.

There is another maneuver that may demonstrate adherence of the tumor to the skin. This consists of gentle compression of the breast substance to make it rounded over the tumor. Where there is no adherence, the contour of the breast will be smoothly round. On the other hand, with any adherence of the tumor to the skin, there is at this point, some flattening of the skin or even obvious retraction.

The examination is then completed by milking the

From the Department of Surgery, Mount Sinai School of Medicine (CUNY) and the Breast Service, The Mount Sinai Hospital, New York, N.Y. 10029.

Requests for reprints should be sent to: Gerson J. Lesnick, M.D., 3 East 76th Street, New York, N.Y. 10021.

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nipples to note whether or not any discharge can be expressed from them.

This examination will uncover any of the following signs: 1) a tumor, 2) retraction of the skin, related either to a palpable tumor or one that cannot be felt, 3) erythema, 4) edema of the skin over a portion of the breast, or the entire breast, and 5) discharge from the nipple.

Differential Diagnosis of a Tumor in the Breast

Normal breast parenchyma is not completely smooth and of uniform consistency. Parenchyma is nodular and is distributed in a lobular fashion with individual breast lobes radiating out from the nipple toward the periphery. The lobes of denser parenchyma are separated by fat. The margin between the fat and the denser breast substance gives the breast an irregular contour. This normal lobulation is usually, but not always, bilaterally symmetric. The lobe extending toward the upper outer quadrant of the breast is usually the firmest and most nodular part. However, normally it is firm rather than hard, and quite mobile. The nodularity of the breasts changes in response to estrogen stimulation. In the part of the menstrual cycle, when more estrogens are produced, parenchyma grows and breast vascularity increases. Then the parenchyma becomes more nodular, and the individual nodules may become tender. These changes regress with the onset of menses, so that the breast is softest and nodularity is at its minimum about one week after menstruation begins. A patient with a tender nodule premenstrually should be reexamined following her period to see whether the lesion persists or regresses completely. If it does regress completely, one can be fairly sure that it was no more than a physiologic response to estrogen stimulation. Differentiating such physiologic lobulation from a true tumor may tax the abilities of even an experienced examiner. In such instances, aides such as mammography and fine-needle aspiration cytology can be of help.

Cyst

Most often a tumor in the breast appears as a distinct nodule that is obviously different from the underlying nodularity. The most common discrete tumor in a woman during her actively menstruating life is a cyst. This tumor is found in women from the approximate age of thirty to the menopause. The cyst may appear as a distinct, rounded, mobile, rather firm tumor, or a diffuse, firm-to-hard induration in the breast. The texture and outline of the cyst depend upon its depth in the breast substance and the consistency of the surrounding breast tissue. Cysts may be single but are frequently multiple, and may be of any size from microscopic, containing no more than 0.10cc of fluid to a size containing as much as 500cc of fluid. Several cysts may exist at one examination. Other cysts can appear a short time after cysts have been aspirated. The diagnosis of a cyst can be confirmed by aspiration, which will also cure the individual cyst. Every cyst must be aspirated individually, whenever it appears. Cyst fluid is clear or slightly opalescent. The color varies from pale amber to dark green. If cyst fluid is not bloody, cytology is not necessary since the fluid is acellular. (Bloody fluid may indicate the presence of an intraductal papilloma or intraductal papillary carcinoma and requires excision of the lesion. Aspiration of such a lesion often leaves a residual palpable mass.) Often, following aspiration of large cysts, one can feel a rim of indurated surrounding breast tissue secondary to compression of breast tissue by the cyst. This will subside in a few days. All patients exhibiting this phenomenon should be examined a week later to be sure that the breast has returned to normal. Any residual masses palpable at the second examination must be diagnosed individually by aspiration or, if they cannot be aspirated successfully, by excision. Patients that have cysts should be told that each cyst must be aspirated in order to determine its nature, since the nodule thought to be merely another cyst and left untreated too often turns out to be a carcinoma.

Fibroadenoma

Fibroadenoma of the breast is the most common tumor occurring in women from the age of the menarche to about age 35. These tumors are much less frequent thereafter, although occasionally they are seen even in women past the menopause. The presumption is that the tumor existed undetected since the third decade in the patient's life. A few fibroadenomas have the consistency of normal breast tissue and are noted only when the patient is older, on a routine mammograph where they mimic a cyst. The physical findings of most fibroadenomas follow a set pattern. The tumor is very well circumscribed and quite mobile. It has a rubbery consistency. To the uninitiated, this consistency resembles that of a cyst. They usually grow quite slowly although occasionally, particularly during pregnancy, they do grow rapidly. All of these tumors should be excised. They grow, although slowly, and whenever they are excised, the size of the incision will depend upon the size of the tumor. Occasionally the differential diagnosis between a fibroadenoma, a cystosarcoma phyllodes, and a medullary carcinoma can be difficult if not impossible. All three of these lesions may be identical on physical examination and mammography. Cystosarcomas usually grow quite rapidly and attain quite a large size, but the growth rate may be slower. Medullary carcinoma can show some signs of adherence on physical examination, and may show some irregularity on mammography. However, in some cases, neither of these phenomena is present and the lesion can precisely mimic a benign fibroadenoma. In older patients, the lesion must be treated with still greater suspicion.

Rare Lesions

Lipoma: Lipomas of the breast have the same characteristics as lipomas located anywhere else.

Granular Cell Myoblastoma: This tumor is usually small. In its clinical features it resembles a carcinoma in that it is not sharply demarcated and may show some retraction signs. When excised and examined grossly, it may resemble a carcinoma. The tumor contains a large number of granular cells. Its histology is quite characteristic and it is benign.

Cystosarcoma Phyllodes: This tumor resembles a fibroadenoma on physical examination. It is usually distinctly larger and characterized by a history of rapid growth. It may be benign or malignant. The clinical behavior may not parallel the histological features. Lesions that appear malignant histologically may behave benignly and vice versa. These tumors do not spread to the axillary lymph nodes. The malignant ones spread systemically by vascular invasion. The most common site of metastases is the lung. The benign lesions can be controlled by an adequately wide local excision, although some of the larger ones may require mastectomy in order to leave an ample margin of normal tissue around the tumor. Recurrence is usually local and will respond to further excision.

Sclerosing Adenosis: This lesion appears as an ill-defined tumor in the breast. At operation, it may resemble a carcinoma on gross examination. The histologic pattern, too, bears a superficial resemblance to that of an infiltrating cancer, and a frozen section may deceive an inexperienced pathologist. The lesion is benign.

Sarcomas: Sarcomas of the breast are rare but do occur. The most common sarcoma is a lymphosarcoma. The clinical features of this lesion are almost indistinguishable from a carcinoma. The tumor can be treated either by excision or by radiotherapy.

Cancer of the Breast

Cancer of the breast is the most common breast tumor in women who are postmenopausal. It is quite rare for someone under the age of 25. Approximately 0.5% of breast cancers occur under the age of 30, and approximately 3% under the age of 35. The clinical features of a carcinoma of the breast may resemble those of the benign tumors described above but, more often, the tumor appears as an ill-defined mass that is quite hard and displays adherence to the overlying skin or the underlying fascia. Skin adherence can be demonstrated by the maneuvers mentioned above. Even quite small tumors will often display adherence to the overlying skin. Occasionally cancers of the breast can be confused with cysts, but an attempt at needle aspiration will differentiate the solid cancer from the fluid cyst.

Differential Diagnosis of Skin or Nipple Retraction

Cancer: Skin or nipple retraction strongly suggests an underlying carcinoma.

Periductal Inflammation: Periductal inflammation secondary to duct ectasia is the most common benign lesion associated with skin or nipple retraction. The lesion shows up as a mass, is usually tender, and often erythematous. It is located at the edge of the areola. It is due to bacterial infection of terminal ducts that have undergone squamous metaplasia with accumulation of material in the ducts. It can be treated by incision and drainage, but this will often result in a persistent recurrent nipple fistula. The diagnosis can be established by aspiration through a relatively wide-bore needle (18 gauge). A small drop of pus is diagnostic. The material can be cultured and tested for sensitivity to antibiotics. The infection usually responds promptly to antibiotics, although some induration may persist for as long as six weeks. Failure of prompt resolution or the persistence of induration indicates the need for excisional biopsy.

Fat Necrosis: Trauma that causes a large hematoma, or fat necrosis, can also result in skin retraction due to fibrosis during the healing process. One must observe extreme caution in attributing retraction to a hematoma or fat necrosis since trauma often calls attention to a neoplasm that was present although not noted prior to the injury. The trauma has to be substantial and significant and of a grade sufficient to cause a severe contusion. The diagnosis of fat necrosis can sometimes be confirmed by aspiration of liquid fat. Persistence of a mass after resolution of a hematoma indicates the need for biopsy.

Mondor's Disease: Mondor's Disease is another lesion that grossly resembles skin retraction. The lesion is a vasculitis of subcutaneous vessels. The vessels can be veins, small arterioles or lymphatics. It is seen as a tense, somewhat tender cord adherent to the overlying skin, causing retraction of the skin with any motion that tenses the cord. This produces a crease on the side of the breast when the arm is raised. Frequently the vessel extends downward across the breast from the axilla onto the skin of the lower anterolateral thorax, following the course of the thoracoepigastric vessels. Similar lesions can be noticed in the upper arm following mastectomy. These are due to sclerosis of lymphatics. This affliction is self limited and will subside spontaneously in four to six weeks.

Differential Diagnosis of Nipple Discharge

Some patients seek care because they have noticed discharge from the nipple. The discharge may come from one duct or from several ducts, and is clear, opalescent or milky, pale yellow, green or brown in color, serous or bloody. If the discharge comes from several ducts and is either somewhat cloudy, milky, or greenish, it is of no consequence and does not indicate breast disease. Some greenish discharge is so dark it seems to be brown or black, and may be confused with blood. When a few drops are placed on a piece of gauze the true color is immediately apparent. Bloody discharge that comes from a single duct, either old blood or fresh blood, or discharge which is clear and the color of serum, indicates the presence of an intraductal papillary tumor. When associated with a palpable mass, the tumor is almost invariably a papillary or intraductal carcinoma. If no tumor can be felt, the tumor is almost always a benign intraductal papilloma. These lesions cannot be seen on mammography. They are readily removed through a circumareolar incision by dissecting up the areola, locating the subareolar ducts, and excising the duct which is filled with the secretion.

Occasionally one sees patients with a profuse milky discharge indicating galactorrhea. It may be secondary to a pituitary adenoma, but more often it is idiopathic. The differential diagnosis of the causes are beyond the scope of this article. Small amounts of milky secretion from several ducts may be present in patients soon after pregnancy, and in some patients when contraceptive medication is stopped after taking it for a long time. The discharge is of no consequence and will subside if stimulation of the nipple is avoided.

Eczema of the Nipple—Paget's Disease: Eczematoid changes in the skin of the nipple are readily detected on physical examination. Most often there is no associated palpable tumor, and no lesion is visible on mammography. Eczema that involves the nipples is almost always due to an intraductal cancer. Diagnosis is established by biopsy of the nipple. A small sliver of the eczematous skin is removed under local anesthesia.

Techniques of Establishing a Diagnosis

The diagnostic impressions based on physical examination can be confirmed in a number of ways. A tumor that can be aspirated is definitely a cyst. If the tumor is solid, then suction from the syringe will bring into the needle a small amount of material for cytologic examination. Examination must be done by a cytologist experienced in the method. The aspiration requires a needle of 18 or 20 gauge. Finer needles will not obtain sufficient material. The fluid must be smeared and fixed promptly, since fine cellular detail is lost if the smear is allowed to dry.

When the diagnosis is almost certainly carcinoma and it has been decided to use methods other than immediate operation, the diagnosis can be confirmed by examining a core of tissue obtained by a large-bore biopsy needle. The specimen is processed as any other material or histologic examination.

Mammography: Mammography is helpful not only in the detection of occult tumors, but also in the differential diagnosis of palpable lesions. It is particularly useful in detecting and diagnosing tumors in elderly women with large fatty breasts. It is less accurate in younger women whose breasts are dense and opaque to x-ray. Accurate interpretation of mammograms requires knowledge of the limitations of this method. Tumors at the periphery of the breasts, in the extreme lateral or medial, inferior or superior portions of the parenchyma and close to the chest wall, may not be detected in x-ray examination. In women with relatively dense breasts, subareolar tumors may not be seen. In young patients with small, dense breasts, the mammogram may fail entirely to demonstrate a tumor. Mammograms cannot reliably distinguish cysts, fibroadenomas, cystosarcoma phyllodes, and medullary cancer from each other. To say that a tumor is benign according to the mammogram is insufficient. The tumor must be excised and the tissue examined histologically.

The chief utility of mammography is in the detection, in women over 45 years of age, of tumors that are not palpable. These lesions may appear as a small stellate shadow deep in a rather large breast. In other cases they are indicated by a group of very fine dust-like calcifications in an otherwise apparently normal breast. Most of the calcifications seen in mammograms are associated with benign conditions and only radiologists experienced in such diagnoses can make the differential diagnosis of their significance.

Clinical Staging of Breast Cancer

Clinical examination goes beyond detection and diagnosis of breast cancer. Clinical examination supplies information used to stage the tumor, to categorize it for prognosis, and to select the appropriate treatment.

Clinical staging of breast cancer uses the indexes of tumor size, evidence of involvement of the skin or the chest wall, the presence of palpable axillary or supraclavicular lymph nodes, and the characteristics of any nodes present. In addition, staging varies according to the presence or absence of evident distant metastases.

The clinical staging system in widest use is that of the International Union Against Cancer and The American Joint Committee on Cancer Staging and End Results

Reporting. This is the so-called TNM System of Clinical Staging. T refers to tumor, N to nodes and M to distant metastases.

The T Classifications are:

TIS—In situ lesions
T0—Tumors that are not palpable
T1—Tumors less than 2 cm in diameter without any evidence of skin or chestwall involvement. They may display adherence to the underlying pectoral fascia or dimpling of the skin. Those without adherence to fascia are classified T1A and those with adherence T1B
T2—Tumors 2 to 5 cm in diameter, also without evidence of skin or chestwall involvement. Similarly, they can be classified as T2A and T2B depending on whether or not they adhere to the pectoral fascia.
T3—Tumors more than 5 cm in diameter are similarly divided between T3A and T3B, depending on fixation to the underlying pectoral fascia
T4—Tumors that display involvement of the skin or chestwall.
 T4A tumors show fixation to the chestwall, that is to the ribs, the intercostal muscles, or the serratus anterior muscle.
 T4B—tumors with edema of the skin (including peau d'orange), ulceration of the skin of the breast or satellite skin nodules confined to the same breast.
 T4C—tumors show fixation to the chestwall as well as skin changes.

The N Classifications are:

N0—No palpable homolateral axillary nodes
N1—Movable, palpable, homolateral axillary nodes. This classification is divided into N1A, nodes not considered to contain growth, and N1B, nodes considered to contain growth.
N2—Homolateral axillary nodes considered to contain growth and fixed to one another or to other structures.
N3—Cases with homolateral supraclavicular or infraclavicular nodes thought to contain growth and patients with edema of the arm.

The M Classifications are:

M0—No evidence of distant metastases
M1—Distant metastases present. Any involvement beyond the breast area is considered a distant metastasis

These Categories are then grouped into Stages in the following way:

Stage I consists of T1 plus N0 or N1A, that is tumors less than 2 cm in diameter and nodes considered to be free of tumor.

Stage II includes tumors between 2 and 5 cm in diameter, as well as tumors associated with palpable axillary nodes thought to contain tumor but which are not fixed to each other. In other words, any T2 tumors and T1 tumors which have N1B.

Stage III includes all more advanced tumors that are not Stage IV, that is any T3 or T4 tumor and any N2 or N3 tumor.

Stage IV is any tumor with M1, distant metastases.

Stage I tumors usually have a very good prognosis. These are the tumors for which some treatment less than mastectomy may be feasible. Stage II tumors comprise the bulk of operable breast cancers that are treated in the conventional way, by modified or radical mastectomy. Stage III tumors are locally advanced and have a bad prognosis because there are usually occult metastases. Treatment for this group of patients should probably be different than for Stage II tumors.

Surgical Treatment of Breast Cancer

The surgical treatment of breast cancer remained unchanged for half a century after Halsted and Willy-Meyer described the operation of radical mastectomy in the last decade of the nineteenth century. All patients with breast cancer were treated by radical mastectomy. Some patients received radiotherapy as well and those considered inoperable were treated solely by radiotherapy. During the past 30 years the heretofore set approach has been challenged, and many other therapies have been suggested. New operations have been suggested, some less extensive and others more extensive. In addition, radiotherapy alone has been suggested as the treatment for some early breast cancer.

To cure any cancer, all portions of the tumor must be excised or destroyed. Since a cancer generally begins in one site and later spreads locally through lymphatic and vascular channels to invade other regions, there is a time when the entire lesion can be circumscribed by an adequate excision. The problems are to determine which patients have localized disease amenable to such treatment and to devise an operative procedure that removes all of the tumor without causing undue deformity and disability. For tumors that have spread beyond the local site, appropriate systemic therapy is required. The categories of clinical staging provide a rough index of likelihood of systemic spread.

Stage I breast cancer treated by radical mastectomy results in a 10-year disease-free survival of 75%. For Stage II tumors, the 10-year disease-free survival rate is about 60%, and for Stage III, the rate is less than 10%. Prognosis can be further refined by histologic examination of excised axillary lymph nodes. When nodes are free of tumor, 75% of the patients are free of disease at the end of 10 years regardless of the size of the primary tumor. When one to three nodes are involved with tumor, this percentage drops to 60% and when four or more nodes are involved, only about 25% of patients are free of disease at the end of 10 years. This means that 75% of patients with four or more affected nodes have disseminated disease at the time that they are first treated.

For patients with Stage II disease, that is, patients who have tumors between 2 and 5 cm in diameter, or patients whose axillary nodes are palpable due to apparent invasion by carcinoma, only an operation which removes the entire breast and the axillary lymph nodes is adequate. The entire breast must be removed because the primary tumor spreads diffusely in the breast tissue and is often multicentric. Multicentricity has been demonstrated frequently on whole-organ sections of excised breasts. Axillary nodes must be removed since palpation of the axilla is inexact and 30% of axillae that are felt to be disease-free will demonstrate evidence of tumor in axillary nodes. The operative procedure should remove tumor in the nodes that can otherwise act as a secondary locus for further dissemination. In addition, examination of the nodes gives necessary information about the extent of axillary involvement, helping to determine the necessity of any adjuvant systemic therapy for the treatment of occult metastases. These objectives can be achieved through either the standard radical mastectomy or the modified radical mastectomy, in which the entire breast, including the pectoral fascia, and all axillary nodes are removed, but the pectoralis major muscle is left in place. At present, some radiotherapists suggest that patients with Stage II disease can be treated just as well by local excision of the tumor followed by radiotherapy to the residual breast, the axillary and internal mammary lymph nodes, and the supraclavicular fossa. The only controlled clinical test of this thesis demonstrates that results of such therapy are distinctly inferior to those achieved by radical mastectomy.

For Stage I and III disease, treatment can be modified. In Stage I disease, the incidence of axillary-node involvement is low. For this reason, operations less extensive than mastectomy and axillary dissection have been suggested, either with or without adjuvant radiotherapy. Some types of breast tumors, comprising approximately 10% of all breast cancer, are circumscribed and have a relatively low potential for spread. These are localized papillary cancers, small medullary cancers, colloid cancers, tubular cancers, and infiltrating ductal cancers less than 5 mm in diameter. The cure rate for such tumors treated by radical mastectomy is about 90% to 95%. If the patient is willing to accept an approximate 20% to 25% risk of recurrence, which would require a more extensive procedure subsequently, and that may be associated with an increased risk of mortality and morbidity, segmental mastectomy or simple mastectomy can be done. Some radiotherapists suggest the addition of radiotherapy to this regimen. When there is not evident spread, this seems excessive. It seems more logical to remove the axillary nodes and then give additional treatment only to patients with axillary-node involvement. Intraductal cancers, which are among those that can be detected by mammography even when they cannot be palpated, are not suitable for this treatment since intraductal lesions are frequently multicentric throughout the breast.

Some plastic surgeons suggest subcutaneous mastectomy and the placement of an implant as treatment for minimal cancers and for various precancerous mastopathies. This operation can only be condemned. It is inadequate for treating cancer, since all breast tissue cannot be removed, and cancers have been reported following the operative procedure. The surgical results are not pleasing cosmetically and may be inferior to those achieved by mastectomy and subsequent reconstruction. The operation is obviously too drastic for patients who do not have cancer.

Patients with Stage III tumors are not curable by surgery alone. Their disease requires some additional therapy instead of, or in addition to, an operative procedure. Since almost all these patients will develop systemic recurrence, systemic therapy is needed. At present chemotherapy and hormone manipulation are the most suitable treatments. Since chemotherapy is more effective if the total body tumor burden is smaller, it is helpful to remove the tumor and involved nodes surgically as part of the therapeutic regime. Radiotherapy is insufficient for this purpose. Most radiotherapists have noted a much higher recurrence rate among patients with large tumors treated solely by radiotherapy. They report better results for radiotherapy when added to excision of the tumor.

The same considerations apply to patients with Stage IV disease, patients with demonstrable systemic metastases. In this instance, however, local excision of the tumor may be of little help since the sum of tumor mass in distant sites may well exceed the tumor mass at the local site, precluding useful surgical debulking.

In summary, proper treatment of breast cancer requires careful clinical staging and is different for each stage.

Stage I tumors, those less than 2 cm in diameter and without axillary adenopathy, can be treated by partial mastectomy of simple mastectomy plus lower axillary dissection. Postoperative radiotherapy can follow segmental mastectomy immediately or can be withheld for a possible recurrence. The recurrence rate is about 20% to 25% in patients treated by segmental mastectomy alone. Alternatively, they can be treated by modified radical mastectomy.

Patients with Stage II tumors should be treated by mastectomy and axillary dissection. This can be accomplished by a standard radical mastectomy, but modified radical mastectomy with preservation of the pectoralis major muscle and removal of the pectoralis minor muscle is preferable. If axillary nodes removed at surgery show invasion, adjuvant therapy (hormone therapy, chemotherapy, or radiotherapy) is indicated.

Patients having medial lesions should have supplemental radiotherapy to the internal mammary lymph node chain.

Stage III tumors require some type of systemic therapy in addition to mastectomy and removal of the bulk of the tumor.

Primarily disseminated tumors or recurrent tumors require treatment by chemotherapy, hormone therapy, or radiotherapy. In general, systemic disease requires systemic therapy, and symptomatic local disease will respond to radiation. Many patients require combined treatment.

Choice of the appropriate modality is facilitated by analyzing the tumor for estrogen receptor proteins. When receptors are present, response to hormone manipulation can be anticipated in about 60% of the patients. If receptor is not present, response occurs in less than 10%. About 75% of tumors respond to cytotoxic chemotherapeutic agents. There is some indication that tumors that lack receptors are more responsive. Whenever a malignant breast tumor is removed a portion of the tumor should be analyzed for receptor proteins since it may not be possible to secure tissue for the analysis when dissemination is present.

Summary

Proper management of breast tumors requires precise diagnosis and staging. Clinical evaluation by physical examination and ancillary procedures permit accurate diagnosis in most instances. Clinical staging guides subsequent treatment and estimates prognosis.

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An Experience with Orthopedic Screening of Normal School Children

JACOB F. KATZ, M.D. AND ALAN J. REICH, M.D.

Abstract

Three hundred and seventy-two (372) school-age children were screened for orthopedic impairments. Thirty children were found to have minimal abnormalities.

A companion set of clinical observations on developmental factors associated with gait were made on the same group. Most of the findings were in agreement with the current literature. Those that appeared at variance or were not previously emphasized were 1) slightly greater average external tibial torsion for the right foot than for the left; 2) increased hip rotations in flexion over that in extension; and 3) 10° increase in hip internal rotation in girls in comparison to that in boys.

Introduction

This paper describes the orthopedic experience during a routine screening physical examination of normal children in a New York City East Harlem parochial elementary school.The ethnic distribution of the school closely parallels the population of the area which is about half Puerto Rican or other Latin American origins, one third black, and the remainder white. Three hundred and seventy-two children in the age range of 6 to 15 years were seen; 169 (45.5%) were males and 203 (54.5%) were females. The breakdown by ages shown on Table I illustrates the numbers of children in the various age groups. The circumstances of the study excluded children under 6 years of age (under school age).

After signed parental consent was obtained, the examination was conducted under the auspices of the Department of Community Medicine of Mount Sinai School of Medicine of The City University of New York. The team included interviewers, technicians for simple laboratory studies, and a group of physicians representing community medicine, pediatrics, and orthopedics. Additionally, dentists, cardiologists as well as nurses from the Bureau of School Health of the New York City Department of Health participated in the survey. The children were seen at their school in a "line of flow" approach, in scheduled rotation, utilizing various assigned stations, spread over several days with considerable help in organization from the school staff. This permitted the rapid screening of many children. The results of the general medical evaluations are not included here.

The orthopedic goals were designed to 1) seek orthopedic impairments unknown to the patient, and 2) evaluate some developmental features of gait as determined clinically by walking attitude, tibial torsion, and hip joint mobility.

Orthopedic Impairments

The largest single contribution came from mild trunk asymmetry in 12 instances. Only one case of clinically significant scoliosis was seen and the child was already under active treatment. One child exhibited mild sternum deformity with pectus excavatum. Four youngsters had prominence over the proximal tibias consistent with Osgood Schlatter's disease but without symptomatology. There was one instance of clinically prominent tibial bowing without ligamentous laxity. Two children were sufficiently loose ligamented to display mild knee recurvatum. Two youngsters had mild contractures following previous trauma, one about the elbow and the other around the shoulder. One child had leg length inequality of 1.5 cm. A few foot deformities were seen: One hallux rigidus without disability, one bunion, and one splay foot. There were no unusual numbers of pes planus and those present were minimal and nonsymptomatic. Two sibling children exhibited cafe-au-lait skin pigmentation and were already under medical observation. One child's appearance suggested Marfan's disease because of the elongated, tapered toes and fingers, without known cardiac or ocular involvement.

Evaluation of Developmental Parameters

Foot Alignment in Gait Pattern: The children were instructed to walk in customary fashion toward, as well

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From the Department of Orthopaedics, Mount Sinai School of Medicine of the City University of New York, New York, N.Y. 10029.

TABLE I

Age Distribution of 372 Children Screened for Orthopedic Impairments

	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	13 yrs.	14 yrs.	15 yrs.
M	9	19	22	24	23	18	21	18	10	5
F	17	24	25	19	19	32	33	17	16	1
372	26	43	47	43	42	50	54	35	26	6

169 males
203 females

372

TABLE II

Distribution of the 30 Children that had Minimal Abnormalities

mild trunk asymmetry	12
significant scoliosis (already under treatment with Milwaukee Brace)	1
"Osgood Schlatter-like" upper tibial prominence (without symptoms)	4
pectus excavatum	1
mild joint contracture (shoulder & elbow, one each)	2
tibial bowing (with stable knees)	1
leg length inequality (1.5 cm.)	1
Genu recurvatum (mild—10°)	2
Cafe-au-lait skin pigmentation (already under medical observation)	2
"Marfan-like" external appearance	1
foot deformities	
hallux rigidus	1
bunions	1
splay foot	1
pes planus-significant	0

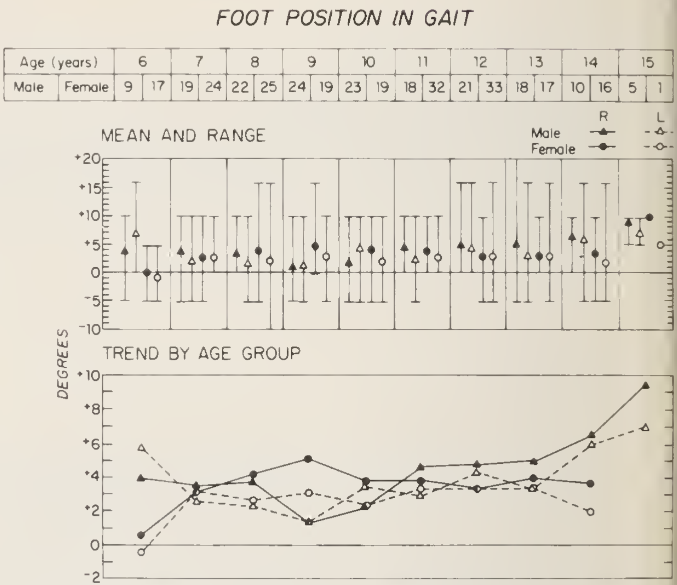

FIG. 1. Analysis of foot position in walking attitude by age, sex, and side. Generally there is outward rotation, slightly more on the right than the left, with some overall increase toward adolescence.

as away, from the examiner. An attempt was made to assess clinically, the rotational attitude of the feet in ordinary gait pattern.

The information was tabulated for yearly intervals from age 6 to 15 separately for boys and girls and separately for right and left feet. The overall average for all of the children was 4° external rotation for the right foot and 3° external rotation for the left foot.

Graphic demonstration of the same information by age for boys and girls is shown in Figure 1.

Foot placement is the final determinant of the interaction of a number of separate contributing elements including tibial torsion, range of hip rotations, and femoral torsion.

Tibial Torsion: Clinical measurement was performed by flexing the knee of the recumbent child and comparing the axis of the maximally dorsiflexed foot with that of the leg when the knee faced directly forward. The overall average was 6.5° external tibial torsion for the right leg and 5° external tibial torsion of the left. Only a small difference was noted in tibial torsion between girls and boys. Figure 2 shows the situation at various age levels.

Femoral Torsion: There is no certain way of determining femoral torsion clinically. Usually specific radiographic techniques have been defined for such measurements (4). At the clinical level, one can use relationships between the ranges of internal and external hip rotations as a rough estimate of femoral torsion. For example, when the range of hip internal rotation is increased over that of external rotation it has been found that there is, at least in children, increased femoral torsion or anteversion (2).

Hip Rotation: Clinical assessments of internal and external hip rotations were made with the children lying supine with hips and knees extended as well as with hips and knees flexed (Fig. 3).

The average of all observations for internal rotation in extension was 31.1° while in flexion, the average was 45.5° (increase of 14.4°).

The average of all observations for external rotation in extension was 39.7° while in flexion, the average was 55° (increase of 15.3°).

Intoeing: A separate analysis was done of 40 (11%) youngsters, 20 male and 20 female, exhibiting unilateral intoeing except for six instances of bilateral involvement. The distribution between side of involvement was 30 left (65%) and 16 right (35%) with representation at all ages (Fig. 4).

Examination of the ranges of femoral hip rotation in these children showed the overall average internal rotation to be 34.6° and external rotation 36.9°. This compared favorably with the entire study group averages of 31.1° and 39.7°.

The tibial torsions of these intoeing children revealed an average of 1.6° external torsion. Compared to the average for the entire study group of 5.7° external tibial torsion (6.5° right leg, 5° left leg) this is a significant reduction and suggested a mechanism for the intoeing.

Discussion

Reports on screening examinations for children at preschool and school ages have presented problems associated with such experiences. Brown described the situation of screening 352 preschool children, between ages two and six, in a low income Spanish-American urban community in the Southwestern United States (1). He made the point that this age group tended to be "the forgotten pediatric age group"—too old for well-baby clinics and not yet old enough for school, in which supervision from nurses and teachers would be likely to result in identification of serious problems. Approximately 5% of the children had chronic physical impairments, of which only three individual children had orthopedic diagnoses—two of tibial torsion and one of scoliosis. Orthopedists were not part of the examining pool.

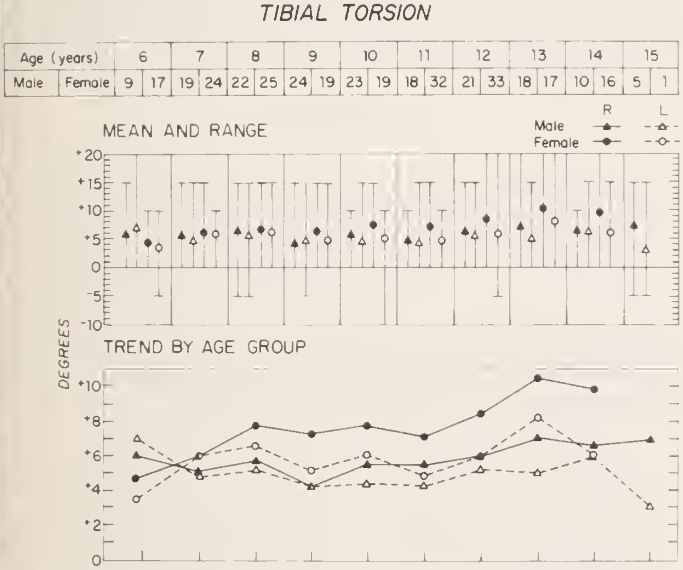

FIG. 2. Analysis of tibial torsion by age, sex, and side. There is a small increase in external torsion of the right leg. Tibial torsion is roughly parallel in boys and girls with small increase in external torsion in girls.

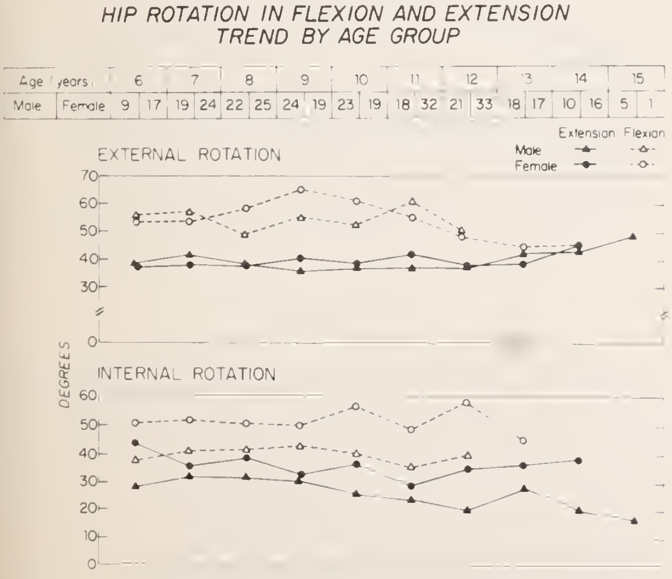

FIG. 3. Analysis of ranges of hip rotations by age, sex, and side. There is gross parallelism except for overall greater ranges in girls.

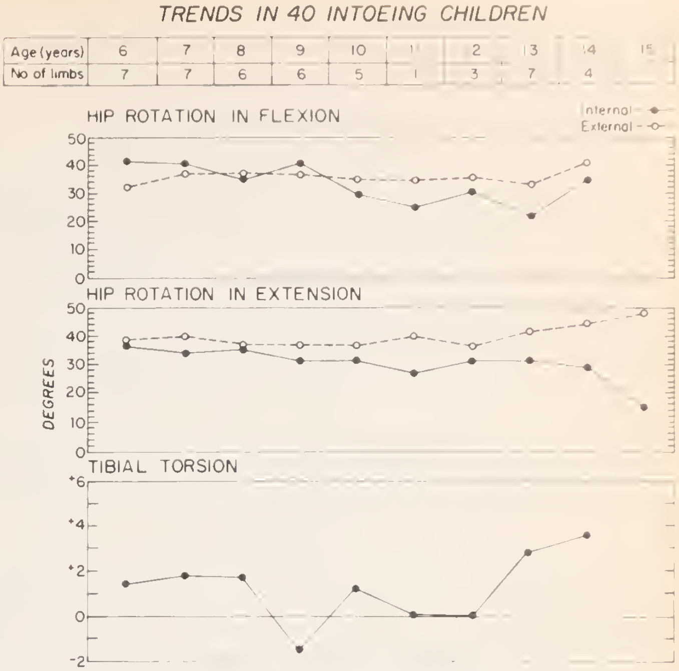

FIG. 4. Analysis of 40 children with intoeing. Hip rotations grossly paralleled the overall averages. Tibial torsion diminished.

Grant, reporting on results of health screening in 6058 school-age children (kindergarten through high school ages), found 13.4% with a previously undetected abnormality (5). The abnormalities in 9.5% of this group were detected by paramedical examination and in 3.9% by physician examination. Of this latter group with vision, learning, urinalysis, and blood pressure abnormalities, 50 (.8%) children had orthopedic abnormalities in which scoliosis and other postural deviations were most frequent. It was believed that this type of review did not warrant being conducted annually and could be done less frequently with benefit. Orthopedists were not included in the primary examining pool in this study. Hensinger reviewed a 10-year experience of orthopedic screening of school-age children (kindergarten through twelfth grade) in the Delaware school system (6). The format that was followed included a preliminary screen by school nurses following a previously prepared checklist. The children with suspected problems were brought to a central location for definitive orthopedic screening. Of the 316,002 children seen in the first screen by the school nurse, 3061 (1%) were selected for the final screen by the orthopedist who then reduced the group to 1461 (0.5%) problems referred for further investigation or treatment.

It was felt that this type of evaluation did not warrant being conducted more often than once every three years. The indirect benefit of providing a source of continuing education for the school nurse and teacher in improving their examining skills was felt to be a very important byproduct of these screening examinations.

Although orthopedists were included in the initial examination team in the present study the yield of orthopedic abnormalities turned out to be relatively low and generally of mild significance. Some explanation of this circumstance was believed relatable to the school environment, generally better parental supervision and concern, and proximity of medical facilities.

The determination of foot alignment in our study, in average mild outtoeing, appeared to be consistent with published studies consisting mainly of adults. Just as in the other studies, the asymmetry between feet, with the greater average angle appearing on the right, was confirmed by us.

Morton defined "angle of gait" as the habitual position assumed by each foot in the line of motion during walking (8). In his study on inhabitants in the Belgian Congo, he measured over a 1000 footprints and determined the average angle to be approximately 7.5°. The largest number of feet (29%) showed an angle between 5° and 10° with the second largest group (25%) falling between 0° and 5°. He found asymmetry with the greater average angle for the right foot and a lesser average angle, usually about 2° less, for the left foot.

Khermosh, examining tibial torsion in young children from newborn to 5 years of age, found the mean torsional angle to be 2.2° in 0 to 3 months age group (7). There was an average rate of increase of 1.3° per year reaching 9.1° in the 4 to 5 year age group.

Engel studied the various factors influencing gait during childhood in a fashion similar to ours using apparently normal children in local schools and newborn nurseries (3). He found tibial torsion to be 7° in the younger children reaching 13° in the older children. In our study, gradually increasing external tibial torsion with age was also evident. This characteristic appeared to be somewhat more prominent in girls. There was slight asymmetry with the right leg showing greater torsion than the left and again more prominently in girls than boys.

Femoral torsion is usually measured by roentgenographic technique. Fabry, in a study performed on 432 normal children from 1 to 16 years of age, found average anteversion to be 24°—ranging from 32° at one year of age to 16° at 16 years of age (4). On clinical review of these normal children, the range of hip internal and external rotations were about equal at 45°. When internal rotation exceeded external rotation, he found that abnormal femoral anteversion was usually present.

Crane's study of femoral torsion found that there was gradual diminution of torsion in childhood (2). He agreed that when femoral torsion was markedly increased, in otherwise unaffected children, there was an associated marked increase in hip internal rotation, and a decrease in external rotational movement.

In our study, the average hip internal rotation in extension was 31° and the average hip external rotation was 39°. This coincided precisely with Crane's findings in his normal group in which the femoral torsion was normal (2). It is not inconsistent to extrapolate this information and to view the hip rotation findings as indirect evidence of normal femoral torsion.

Summary

The orthopedic experiences in a screening examination of 372 normal school children are described. There were 32 (8.6%) instances of abnormalities, mainly minimal.

In addition to screening, data were accumulated on angle of gait, tibial torsion, and hip joint rotations. Although all determinations were derived from clinical examinations, the findings were largely consistent with developmental data previously reported.

1. Angle of gait exhibited an overall average of 4° external rotation for the right foot and 3° for the left.
2. Tibial torsion had an overall average of 6.5° external torsion for the right leg and 5° for the left leg.
3. Hip internal rotation averaged 31° and external rotation 39°.
4. In 40 (11%) children with intoeing, the probable mechanism was due to tibial torsion with lesser contribution from femoral anteversion.

In several areas our findings required special comment.

1. Slightly greater average external tibial torsion for the right foot (6.5°) than for the left foot (5°)
2. Increased hip rotations (14°–15°) when tested in flexion rather than extension
3. Average of 10° increase in hip internal rotation in girls over that obtained for boys

Addendum

As an interesting correlative experience, it might be mentioned that other techniques had been explored for orthopedic consultation in other cooperative community medicine projects. One of these utilized "live" closed-circuit television with instant two-way audio and video communication between pediatric personnel in a satellite primary health facility and an orthopedic surgeon at the base medical center; and another employed delayed orthopedic analysis of videotaped physical examinations performed by nonorthopedic personnel following a set protocol for posture and musculoskeletal performance.

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Ovarian Pregnancy and the Intrauterine Device: Report of a Case and Review of the Literature

STEPHEN J. WILSON, M.D., CHARLES T. MILANO, M.D., AND ANA MARINESCU, M.D.

Since Piver's initial case report in 1967 of an ovarian pregnancy that occurred while an intrauterine contraceptive device (IUD) was in use, several subsequent cases have been reported (1). Pugh's review of the subject in 1973 discussed thirteen primary ovarian pregnancies occurring with an in situ IUD (2). We wish to report an additional case and summarize the English literature to date.

Case Report

A.G. is a 26-year-old woman whose last menstrual period was December 15, 1977. Her prior menstrual history had been unremarkable. She previously had three elective, first trimester abortions, and used a Lippe's Loop IUD for one year. On January 29, 1978, she came to our emergency room complaining of pain for three hours. The pain was bilateral, dull, and intermittent in the lower abdomen, without radiation, accompanied by nausea and one episode of vomiting. She reported breast tenderness for several weeks as well as both frequency of urination without dysuria, and dizziness without loss of consciousness.

Her physical examination revealed vital signs to be stable. Her abdomen was soft with some voluntary guarding. No rebound, masses or costovertebral angle tenderness could be found. On pelvic examination, the cervix was nontender with an IUD string in place. The uterus was of normal size and nontender; the adnexa as well as rectal examination were negative. Laboratory studies showed a hematocrit of 35%, hemoglobin of 12 gm%, and the white blood cell (WBC) count was 11,000 with a normal differential. The erythrocyte sedimentation rate (ESR) was 35 mm/hr. Urinalysis was benign. A cul-de-sac tap yielded 5 cc clotted blood. The patient was admitted for observation.

Reevaluation the following day disclosed no change in the patient's vital signs, pelvic examination or hematocrit. A repeat cul-de-sac tap obtained no blood. However, her urinary choriogonadatropins (UCG) was positive.

With the presumptive diagnosis of an early intrauterine pregnancy and because of the patient's desire to terminate the pregnancy, an uneventful dilation and aspiration was performed after removal of her intrauterine device. A moderate amount of tissue was obtained. The asymptomatic patient was discharged in two days with stable vital signs and a hematocrit of 34.

On routine postoperative evaluation two weeks later in the Gynecology clinic, the patient was without complaint. Review of the pathology report from her original admission revealed no evidence of villi or fetal parts. However, repeat urinary choriogonadatropins was positive. The patient was readmitted with the presumptive diagnosis of an ectopic pregnancy and taken to the operating room.

Examination under anesthesia, as well as a third culdocentisis, revealed no abnormalities. A formal dilatation and curettage (D&C) obtained only scant tissue. Laparoscopy revealed no evidence of hemoperitoneum, a normal uterus with intact fallopian tubes and a normal left ovary. However, an asymmetrically enlarged right ovary with a hemorrhagic component was noted deep in the cul-de-sac. With a tentative diagnosis of ovarian pregnancy, exploratory laparotomy was then performed. No evidence of adhesions or old salpingitis was found. The Fallopian tubes were traced to their fimbriated ends and were found to be free of disease bilaterally. The left ovary was normal on gross examination. The right ovary measured 6x5x4 cm with a smooth surface. It was suspended by the utero-ovarian ligament medially and the infundibulopelvic ligament laterally. The hemorrhagic component occupying the superior pole was shelled out in cystectomy fashion, with conservation of as much ovarian tissue as possible. The operative specimen was opened later, yielding spongy, placenta-like tissue with a 3 mm embryo.

The patient recovered uneventfully and was discharged seven days postoperatively.

Final pathology report described an ovarian mass

From the Department of Obstetrics and Gynecology and the Department of Pathology, Mount Sinai School of Medicine of the City University of New York, New York, N.Y. 10029

Requests for reprints should be sent to: Dr. Charles T. Milano, Department of Obstetrics and Gynecology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029.

TABLE I

Case Reports of Ovarian Pregnancies with IUDs

Author	Age	Parity	Type of device	Months of use	Pregnancy test	Symptoms	Intraabdomen bleeding	Location	Rx
Piver (13)	29	5	Lippe's	not stated	negative	pain, vaginal bleeding, staining	not stated	right	bilateral cystectomy
Stahman (14)	27	1	Lippe's	21	positive	staining, pain	1,500 cc	right	right ovarian cystectomy
Pane	23	Primip	Lippe's	4	negative	staining, pain	1,000cc	right	right ovarian cystectomy
	22	4	Lippe's	9	not stated	staining, pain	1,500cc	right	right ovarian cystectmy
Lehfeldt (16)	21	1	Small Bow	8	not stated	not stated	not stated	left	not stated
	20	1	Lippe's	13	not stated	not stated	not stated	right	not stated
	23	2	Lippe's	12	not stated	not stated	not stated	left	not stated
	27	7	Lippe's	20	not stated	not stated	not stated	left	not stated
	28	5	Lippe's	4	not stated	not stated	not stated	left	not stated
	29	5	Lippe's	8	not stated	not stated	not stated	right	not stated
	29	2	Lippe's	3	not stated	not stated	not stated	right	not stated
	27	1	Lippe's	22	not stated	not stated	not stated	right	not stated
	26	3	Lippe's	8	not stated	not stated	not stated	left	not stated
Bjørn (17)	24	2	Lippe	12	not stated	pain, prolonged menses	2,000cc	right	right oophorectomy
Harris (18)	25	2	not stated	36	positive	discharge, pain	1,500cc	left	left ovarian cystectomy
Helde (19)	39	12	not stated	not stated	not stated	acute abdomen	1,000cc	left	left ovarian wedge resection
Graff (20)	35	5	Beospir	18	not stated	pain	2,000cc	left	left oophorectomy
	not stated	not stated	Lippe's	10	not stated	not stated	not stated	right	right salpingoophorectomy
Varga (21)a	27	2	Lippe's	30	positive-negative	pain, vaginal staining		left	left ovarian cystectomy
b	26	Primip	not stated	36	not stated	not stated large volume of blood		left	
Levin (22)	25	2	Lippe's	6	not stated	pain, irregular bleeding	free blood in abdominal cavity	right	right ovarian cystectomy
Campbell (23)	35	5	not stated	12	not stated	spotting, pain	500cc	right	right salpingoophorectomy
	27	2	not stated	not stated	not stated	pain	300cc	left	left oophorectomy
Pugh (24)	22	2	Lippe's	24	positive	pain	1,000	right	right ovarian cystectomy
Bozza (25)	24	1	Dalkon	18	positive	staining, pain	800cc	right	bilateral ovarian cystectomy
Duckman (26)	28	3	Dalkon	6	not stated	staining	unruptured	left	left oophorectomy
Ledden (27)	28	1	Dalkon	7	positive	pain, spotting	unruptured	right	right salpingoophorectomy
Jonas (28)	not stated								

Darwish (29)	not stated	Multip	Lippe's	24	not stated	pain, menstrual irregularity	not stated	right	ovarian cystectomy ×2
	not stated	Multip	Lippe's	24	not stated	pain, menstrual irregularity	not stated	left	oophorectomy ×1
	not stated	Multip	Lippe's	24	not stated	pain, menstrual irregularity	not stated	left	
Ajjimakorn (30)	29	2	Lippe's	10	positive	pain	400cc	left	left salpingoophorectomy
Fernandez (31)[c]	34	7	Lippe's	13	not stated	staining		left	left salpingoophorectomy
	25	4	Lippe's	24	not	pain	1,000cc	left	left oophorectomy
Rimdusit (32)	22	2	Lippe's	22	not stated	acute abdomen	1,000cc	left	left salpingoophorectomy
Coustan (33)	31	3	Dalkon	15	positive	pain	1,600cc	right (laparoscopy)	right salpingoophorectomy
	26	1	Dalkon	not stated	positive—9 days after suction abortion	none	minimum	right	right salpingoophorectomy
Saber (34)	28	1	Margulies	60	positive	pain	not stated	left	left oophorectomy

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[a] Laparoscopy-swelling of left adnexa (corpus luteum); within one month laparotomy with free peritoneal blood.

[b] Laparotomy ×2: first for suspected perforated corpus luteum cyst with hemoperitoneum treated with right salpingoophorectomy; one month later, reoperated—still using IUD; 1,200cc of free blood treated with left ovarian cystectomy.

[c] Admitted, D&C and removal IUD; readmitted 1 month later with left sided mass—large amount fresh blood and clots.

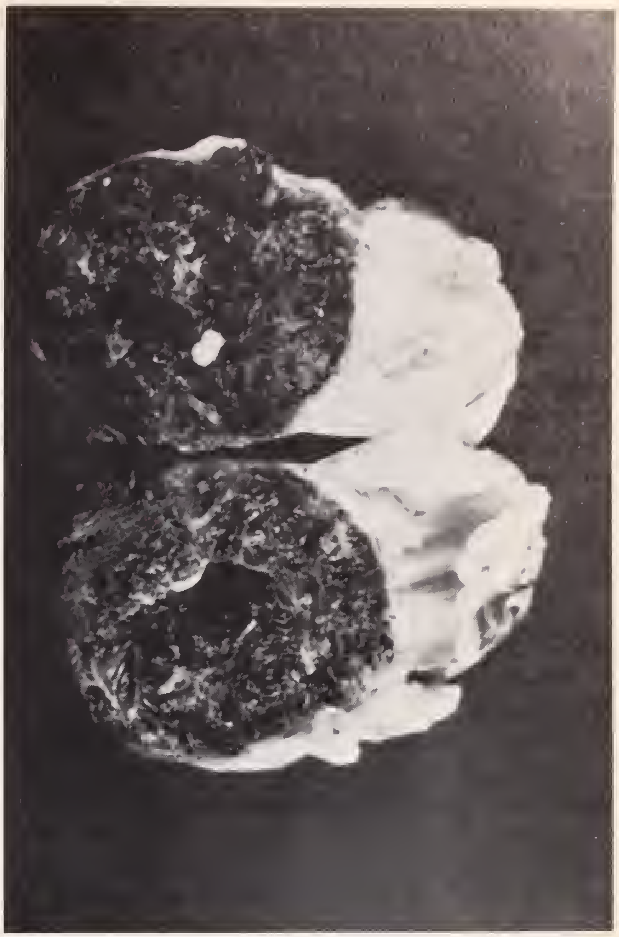

FIG. 1. Gross specimen showing hemorrhagic mass with eccentric cavity.

roughly ovoid measuring 5x3 cm. Its external surface was covered partially by a smooth capsule with no site of rupture seen. Section demonstrated a round, hemorrhagic, 3 cm mass with an eccentric 1 cm cavity (Fig. 1).

The cavity was lined with a smooth membrane and contained a 3 mm embryo. A large, partially cystic corpus luteum of pregnancy was adjacent to this mass. Histologically, a gestational sac was adjacent to the corpus luteum of pregnancy (Fig. 2).

The periphery of the mass consisted of a rim of compressed, ovarian tissue. The sac wall was lined by blood clots and chorionic villi, with trophoblasts infiltrating the corpus luteum (Fig. 3). The diagnosis of extra follicular, unruptured ovarian pregancy was made.

Discussion

Primary ovarian pregnancy is an exceedingly rare event. This is the first reported case from our institution. Spielberg's criteria for diagnosis of an ovarian pregnancy include four components.

The tube on the affected side should be intact. The fetal sac must occupy the position of the ovary. The ovary and sac must be connected to the uterus by the

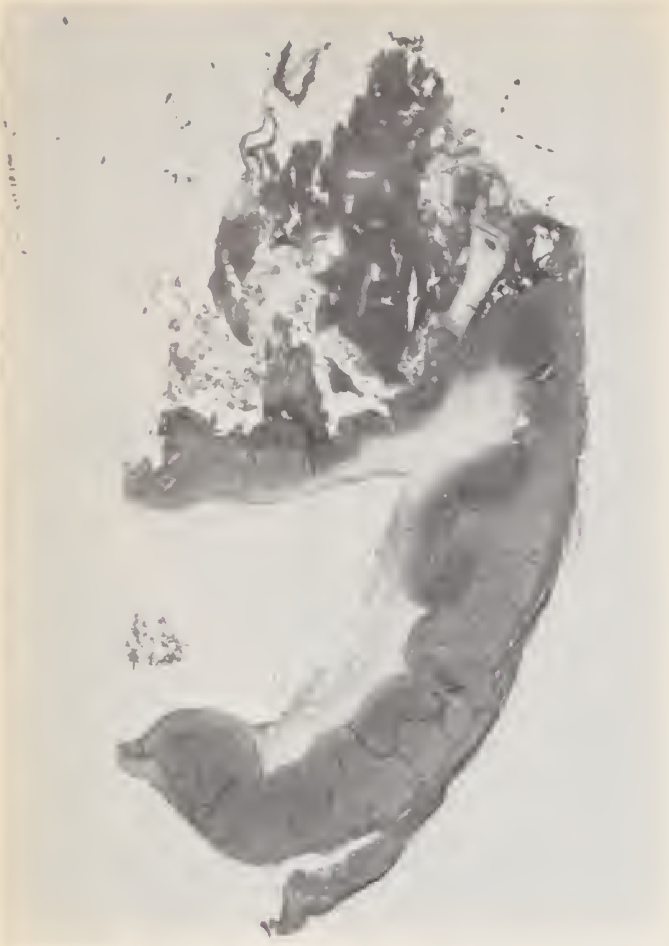

FIG. 2. High-power histological section of gestational sac and adjacent corpus luteum.

uteroovarian ligament. Definite ovarian tissue must be present in the sac wall (3).

Lehfeld's data from the Population Council's Cooperative Statistical Program showed an incidence of one ovarian pregnancy per 40,000 deliveries and a rate of 1.5 to seven ovarian pregnancy cases per 1,000 ectopic pregnancies (4, 5).

The intrauterine device is an increasingly popular form of contraception. As of 1974, an estimated 15 million women worldwide were using an intrauterine device for contraception, with an overall failure rate of 1%–3% (6). Although its definitive mechanism of action in providing birth control remains to be elucidated, several theories have been proposed. They include a local inflammatory response to a foreign substance, enzymatic disturbances, mechanical distortion of the uterus and alterations of prostoglandins or prostoglandin-like substances that affect tubual motility. Whichever theory will prove to be correct, it is likely that these same mechanisms will prove to be responsible for the increased frequency of ectopic pregnancies reported by several authors in patients using an IUD (7, 8). Various estimates of the ratio of ovarian pregnancy to ectopic pregnancy in women using intrauterine devices range from 11% to 24% (9, 10).

In the literature review, thirty-seven cases of ovarian pregnancy occurring in women using an intrauterine device are listed in Table I. Although reviewed here, no attempt was made to analyze these cases for their ability to meet Spielberg's criteria.

Women in this series ranged from 20 to 30 years of age. They had been using an IUD from four to sixty months before developing an ovarian pregnancy. Most were symptomatic with irregular vaginal bleeding or abdominal pain prior to diagnosis. The overwhelming majority had a significant hemoperitoneum at the time of surgery, with only two cases, other than our own, being unruptured ovarian pregnancies. Statistically, no significant laterality was evident. To date, no case of ovarian pregnancy associated with the use of a copper- or progesterone-containing IUD has been reported. Perhaps this is due to the fairly recent introduction of these types of IUDs.

Although ovarian pregnancies are rare events, their diagnosis, particularly in patients using an IUD, may be underestimated or delayed unnecessarily. Complaints of lower abdominal pain or irregular vaginal bleeding in an intrauterine device user are common and often attributed

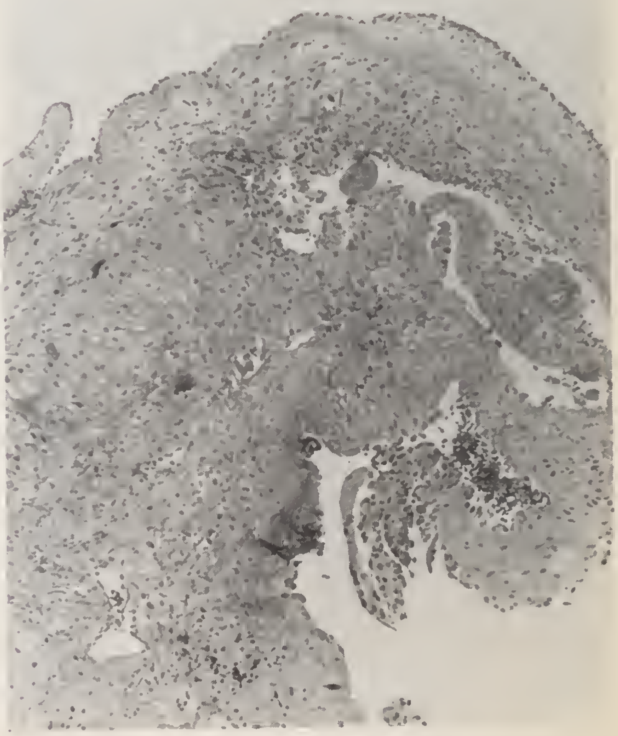

FIG. 3. Low-power histological section of sac wall.

to side effects of the intrauterine device, delaying diagnosis of an ectopic or ovarian pregnancy until rupture occurs. A higher index of suspicion of an extrauterine gestation appears warranted in evaluating complains from an intrauterine device user. Furthermore, careful pathologic examination of all tissue elements obtained during laparotomy for ruptured hemorrhagic corpus luteum cyst, including blood and clots in the peritoneal cavity, and perhaps wedge resection of the involved ovary, could contribute to increased detection of ovarian pregnancy (11, 12).

Further data concerning the relationship of ovarian pregnancy and the use of an intrauterine device must be collected and investigated. Heightened clinical suspicion and more diligent pathologic examination of tissue specimens may establish the true incidence of ovarian pregnancy in patients using an intrauterine device for contraception.

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Collision Tumors: Papillary Mucinous Cystadenocarcinoma of Ovary and Endometrial Carcinoma

CAROL CARIDEO, M.S. AND ALBERTO MARCHEVSKY, M.D.

Abstract

A 68-year-old nulliparous woman with a mucinous papillary cystadenocarcinoma of the right ovary and adenocarcinoma of the endometrium is described. Both neoplasms collided with each other. The literature is reviewed and the histopathogenesis discussed.

Introduction

The presence of multiple primary malignancies in the female genital tract has aroused considerable interest. The incidence has been reported as ranging from 4% to 6.8%. The simultaneous occurrence of independent ovarian and uterine carcinomas is well documented. Ovarian endometrioid carcinoma and endometrial adenocarcinoma are the most common histologic types. The combination of mucinous cystadenocarcinoma and endometrial carcinoma has been reported in only a few instances. The collision of the tumors has not been described. We present a mucinous cystadenocarcinoma of the right ovary and an endometrial carcinoma colliding with each other.

Case Report

A 68-year-old nulliparous white woman was admitted to The Mount Sinai Hospital with complains of weight loss, weakness, lower abdominal pain, and distention.

Physical examination revealed a thin, weak woman in no acute distress. Her vital signs were normal. Her abdomen was markedly distended and tender; 6.4 liters of grossly hemorrhagic ascitic fluid were removed by paracentesis. The fluid was negative for malignant cells.

On palpation, there was a large abdominal mass in the right lower quadrant that extended into the pelvis. On pelvic examination, a large, irregular, immobile tumor filled the entire pelvis and cul-de-sac; the uterus and adnexae could not be distinguished within this mass. There was also marked stenosis of the vaginal canal and infiltration of the cervix and vaginal vault by tumor. No biopsy was performed. The clinical impression was that of an ovarian carcinoma.

The patient continued to accumulate abdominal fluid and exhibited signs of early renal failure. Because of general poor condition, chemotherapy and surgery were not advised. She expired after fifteen days of hospitalization.

At autopsy, there were 3000 cc of hemorrhagic ascitic fluid and a large tumor filling the lower abdomen and pelvis (Fig. 1). The peritoneum was studded with multiple (2 to 5 mm) white, firm nodules. The right ovary was replaced by a 12 x 15 x 10 cm partly cystic and partly solid mass. The inner surface of the multilocular cyst was smooth, except for focal areas of papillary projections, and the lumen was filled with hemorrhagic mucoid material. Histologically, the surface was lined by a single layer of columnar cells with abundant clear cytoplasm containing mucicarmine positive vacuoles. In papillary areas, these cells showed different degrees of atypia and increased mitotic activity. A transition between benign and malignant epithelium was present (Fig. 2). The solid part of the ovarian tumor was adherent to the uterus. It was composed of solid sheets of pleomorphic round cells, some of them containing cytoplasmic mucin. There were many mitotic figures, some of them atypical, and focal areas of necrosis and hemorrhage. The right fallopian tube was adherent to the ovarian neoplasm but not infiltrated by the tumor.

The uterus was enlarged, measuring 16 x 10 x 5 cm. The endometrium was replaced by soft, friable, yellow-white tumor infiltrating the myometrium, cervix, upper third of the vagina, periuterine soft tissue, and left ovary. It also adhered to the right ovarian neoplasm. Microscopically, it was composed of irregular glands lined by tall columnar cells exhibiting a moderate degree of nuclear atypia and mitotic figures (Fig. 3). In some areas

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From the Department of Pathology, Mount Sinai School of Medicine of The City University of New York, New York, N. Y. 10029.

Requests for reprints should be sent to: Alberto M. Marchevsky, M.D., Department of Pathology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, N. Y. 10029.

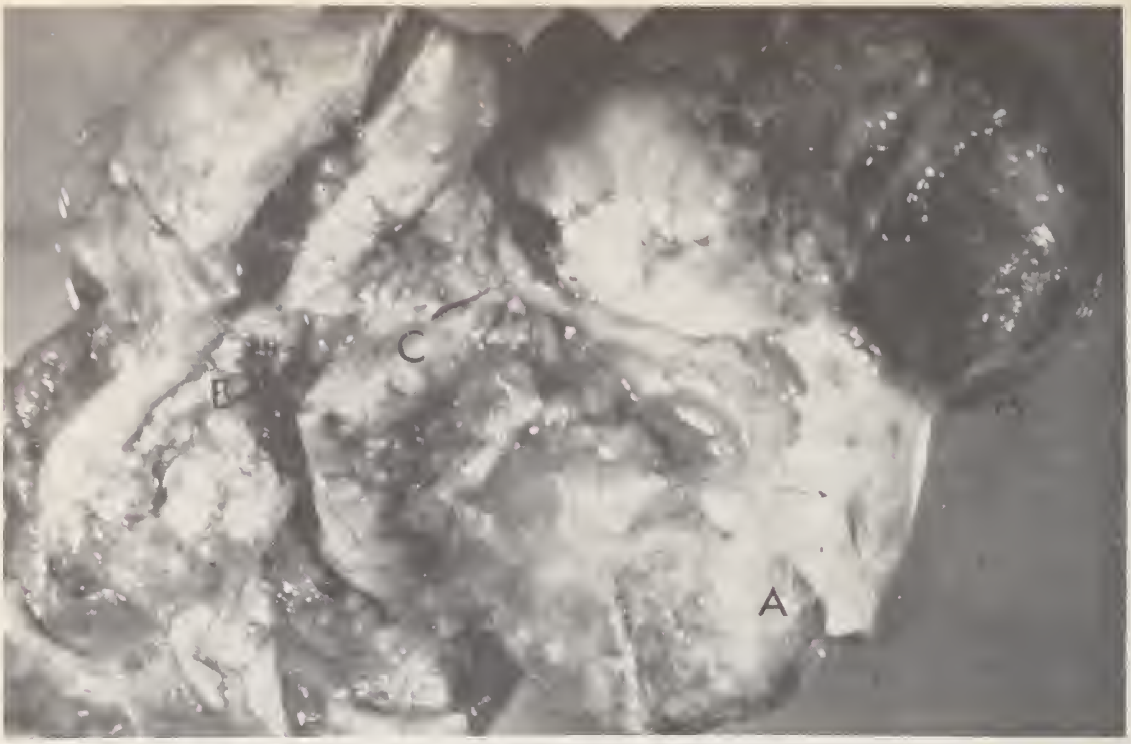

FIG. 1. Photograph of right ovary and uterus showing large ovarian carcinoma (A) and endometrial carcinoma (B) colliding with each other (C).

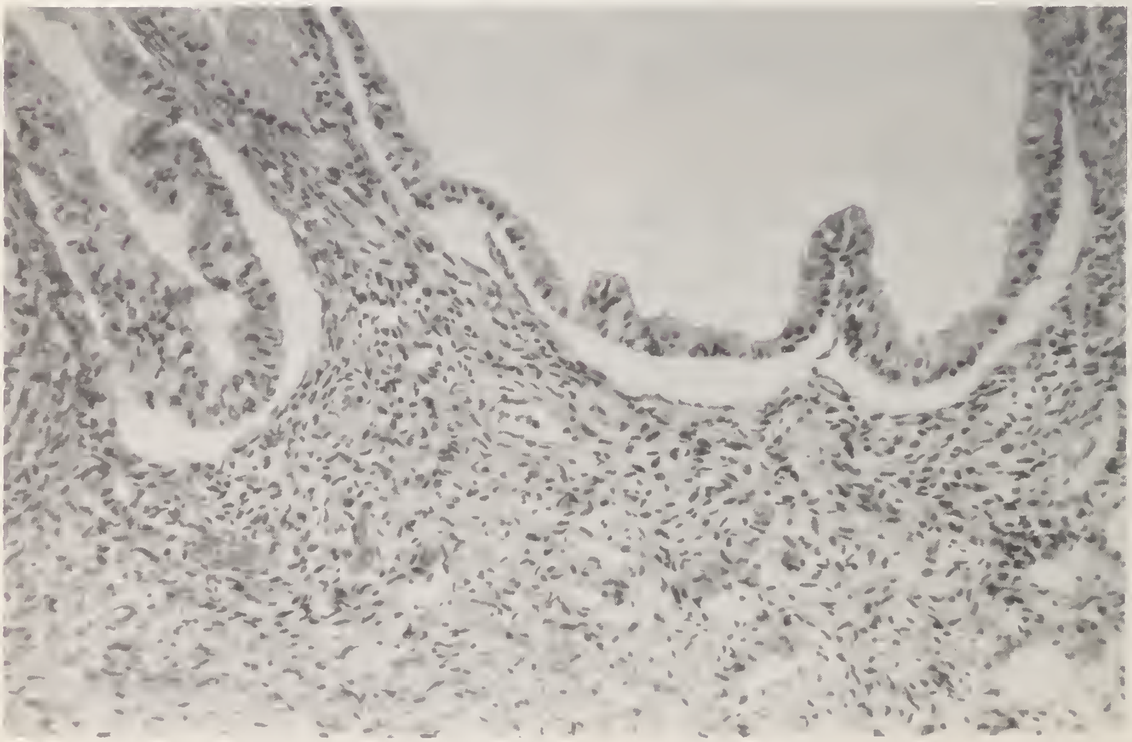

FIG. 2. Photomicrograph of the right ovary showing benign mucinous cystadenoma with transition into carcinoma (H & E, original × 125).

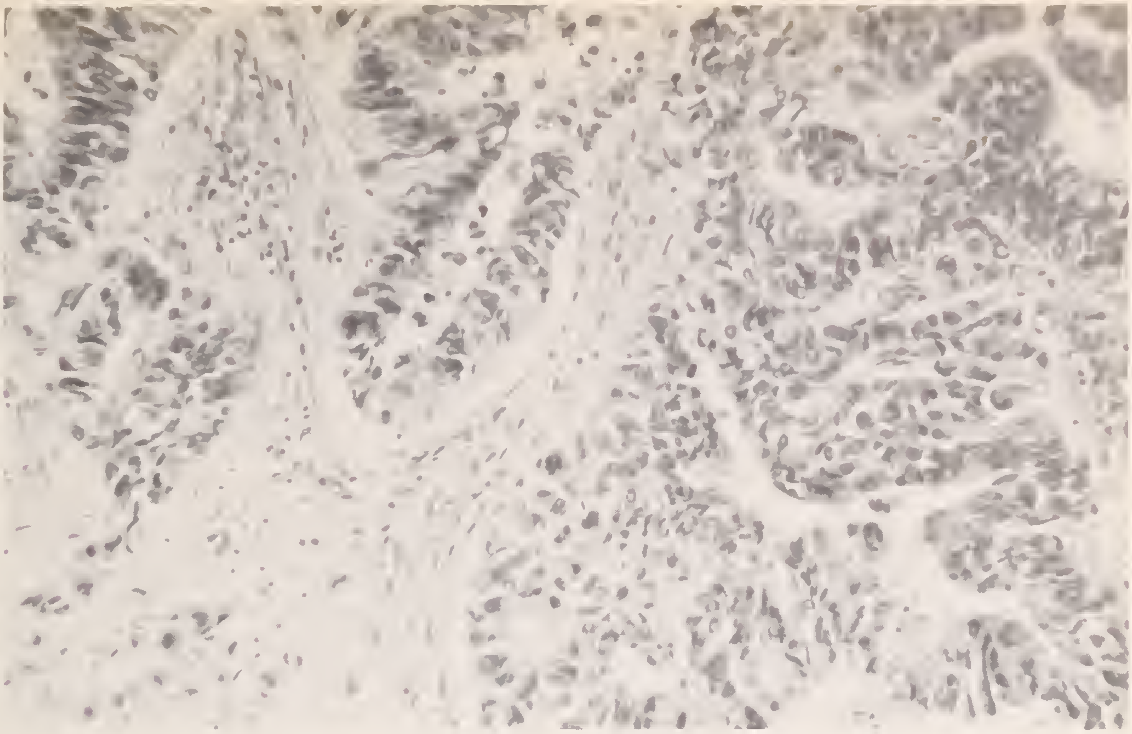

FIG. 3. Photomicrograph of endometrium showing endometrial adenocarcinoma (H & E, original × 500).

there was squamous metaplasia and in others, solid sheets of anaplastic round cells. Mucicarmine stains were negative. Sections from the area where the right ovary was adherent to the uterus showed an intermingling of solid sheets of mucin-secreting cells with glandular spaces.

Our interpretation was that this patient had two independent neoplasms: a well-differentiated papillary mucin-secreting cystadenocarcinoma of the right ovary, and a moderately well-differentiated adenocarcinoma of the endometrium. Both neoplasms collided with each other.

Discussion

The occurrence of multiple primary malignant tumors in the same individual was first described in 1879 by Billroth (1). In 1932, Warren and Gates established three criteria for the diagnosis of multiple malignant primaries: 1) Each tumor must present a definite picture of malignancy; 2) Each tumor must be distinct; and 3) The possibility of one tumor being a metastasis of the other must be excluded (2). Among all patients with malignancies, the incidence of multiple primaries ranges from 0.9% to 6.8% (3–5).

The incidence of multiple primary malignant tumors in the female genital system varies from 4% to 6.8% (6, 7). The most common anatomic sites are ovary and endometrium, ovary and breast, and endometrium and breast. The most common histopathologic types reported are ovarian endometrioid carcinoma, adenocarcinoma of the endometrium, and adenocarcinoma of the breast (6, 8, 9). The combination of mucinous cystadenocarcinoma of the ovary with endometrial adenocarcinoma is rare. As far as we know, it has been reported in only two cases (8). As in several reports, the histopathology of the tumor was not mentioned, this number is probably artificially low.

The histopathogenesis of these tumors has been explained on the basis of their common embryologic origin. The Mullerian paramesonephron develops closely with the coelomic epithelium, so the endometrium and the ovarian stroma originate from the same basic cells. A carcinogen acting on these embryologically related tissues would induce neoplasms that develop either synchronously or metachronously (10, 11).

In 1919, Meyer defined collision tumors as malignant tumors that originate independently of each other at two separate sites and later in the course of their expansion invade each other (12). We were unable to find reports in the literature of collision of two independent neoplasms arising in these organs, despite the anatomic proximity of the ovary and uterus.

Distinguishing between ovarian and endometrial carcinoma as independent primaries may be difficult, but is possible, as in this case, if the histology is clearly different.

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Cancer in Universal and Left-Sided Ulcerative Colitis: Clinical and Pathologic Features

ADRIAN J. GREENSTEIN, M.D., DAVID B. SACHAR, M.D., ANTHONY PUCILLO, M.D., GEORGE VASSILIADES, M.D., HARRY SMITH, PhD., ISADORE KREEL, M.D., STEPHEN A. GELLER, M.D., HENRY D. JANOWITZ, M.D., and ARTHUR H. AUFSES, Jr., M.D.

Ulcerative colitis has long been recognized as a premalignant condition because a considerable proportion of patients with colitis eventually develop colorectal carcinoma at the site of the inflammatory disease (1–7). The incidence of colonic carcinoma in patients with ulcerative colitis has ranged as high as 14% (8).

Certain features are characteristic of colorectal carcinoma associated with ulcerative colitis. Carcinoma develops most frequently in patients in whom the disease is universal and long-standing (3, 5, 9–11). Colitis-related cancers are also said to occur in younger age groups, to be more often multiple, and to carry a poorer prognosis than colonic cancers in the general population (3, 7, 10, 12–15).

In a series of 267 patients with ulcerative colitis treated at this hospital between 1960 and 1976, 30 developed cancer. We have examined the clinical records of the 30 patients in order to elucidate their clinical and pathologic features.

Material and Methods

The records of 300 patients admitted with the diagnosis of ulcerative colitis to The Mount Sinai Hospital between 1960 and 1976 were obtained from the computer files of the institution. On review, 267 proved to be verifiable cases of ulcerative colitis. Our verification of the diagnosis of ulcerative colitis was based on radiologic, endoscopic, and histopathologic criteria. The characteristic features were mucosal inflammation with pseudopolyps and crypt abscesses, continuity of disease and diffuse rectal involvement on sigmoidoscopy in the absence of small bowel disease, severe fistulae, broad fissures, and epithelioid granulomas. Of these 267 patients, 158 had universal colitis and 109 had disease limited to the left side of the colon (that is, distal to the midtransverse colon), as seen in barium enema in all cases and as confirmed at colonoscopy or colectomy in the patients that underwent these procedures (Fig. 1). Among the 267 patients, 30 (11%) developed cancers, of which 26 were colorectal and four extraintestinal. These 30 patients constitute our present series. We have obtained complete follow-up data to 1976 or to the time of death in 29 of the 30 patients.

Results

A) Sex, Age of Onset, and Disease Duration: Of the 30 patients with cancer, 18 were male and 12 female. All four patients with extraintestinal cancer were male, leaving a M:F ratio of 14:12 among the patients with colorectal cancer. This was not significantly different from the 138:129 M:F ratio in the total series of 267 patients. The mean age at onset of ulcerative colitis was 26 years, and the range 16 months to 59 years (Fig. 2). Eleven of the 30 cases had developed ulcerative colitis before the age of 20, and four of them before the age of ten. The mean age at onset of carcinoma was 51 years. The earliest age at which cancer developed was 19 years, after which there was a fairly uniform incidence during each decade of life with a slight tendency to an increase in the older age groups (Fig. 3).

The intervals between onset of ulcerative colitis and development of colorectal cancer ranged from eight to 45 years with a mean of 24 years (Fig. 4). Twenty-one of the 26 patients with colorectal cancer had universal colitis, and five patients had left-sided disease (Fig. 1). In the group with universal disease, the mean duration between diagnosis of ulcerative colitis and carcinoma was 23 years, compared with 32 years in patients with left-sided disease.

B) Type and Distribution of Cancer: Of the 30 patients in this series with cancer, 26 had colorectal tumors, all infiltrating adenocarcinomas. The total number of sepa-

From the Departments of Surgery, Biostatistics, Pathology and Medicine, Mount Sinai School of Medicine of The City University of New York and The Mount Sinai Hospital, New York, N.Y. 10029.

Requests for reprints should be sent to: Adrian J. Greenstein, M.D., Department of Surgery, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, N.Y. 10029.

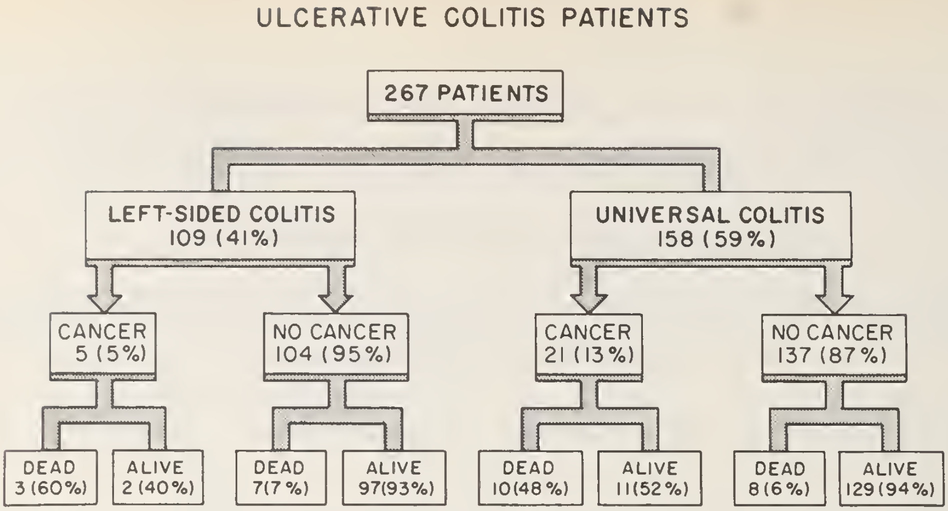


FIG. 1. Overview of the 267 ulcerative colitis patients in this series, analyzed with respect to universal vs. left-sided disease, cancer vs. no cancer, and mortality vs. survival.

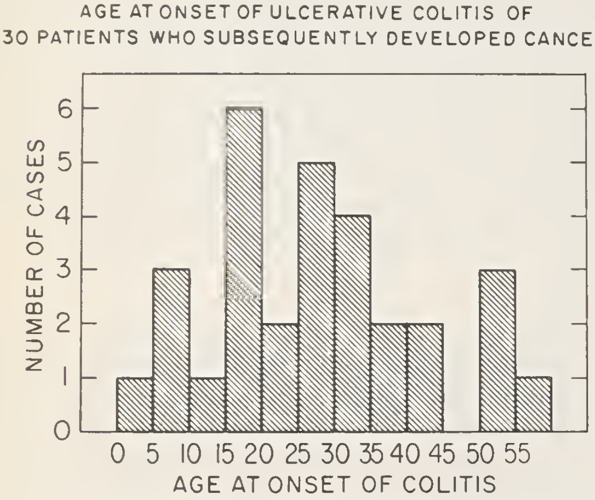


FIG. 2. Ages at onset of ulcerative colitis in 30 patients with cancer. The mean age is 26 years (range 16 months to 59 years).

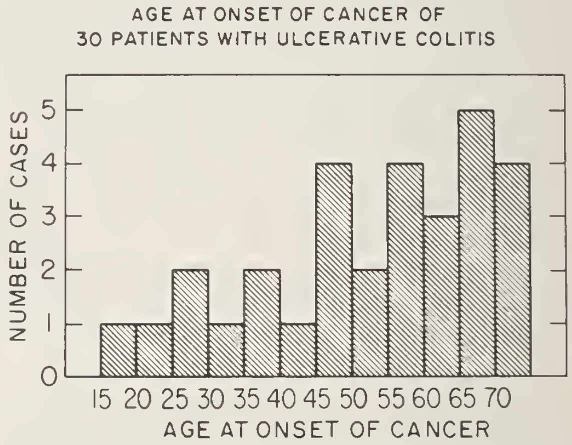


FIG. 3. Ages at onset of cancer in same 30 patients represented in FIG. 2. There is a tendency for more of the cancers to appear in older patients.

rate colorectal cancers in these 26 patients was 29, with two of the patients having multiple lesions. In one patient, three cancers were found—one each in ascending, transverse, and descending colon. In another patient, cancer was found both in the cecum and the rectum. In a third patient, in addition to a solitary cancer, there were multiple polyps and multiple areas of carcinoma in situ noted throughout the colon and within the polyps. The cancers showed a fairly uniform distribution throughout the colon (Fig. 5). Their locations follow:

Ascending colon	8 (28%)
Transverse colon	7 (24%)
Descending colon	4 (14%)
Sigmoid colon	3 (10%)
Rectosigmoid	4 (14%)
Rectum	3 (10%)

Twenty-five of the 26 patients with colorectal cancer underwent operations. The remaining patient had malignant ascites and refused surgery. Four lesions were unresectable because of either local or widespread metastases. Resection was performed in the remaining 21 patients. In 15 cases, the surgeons considered the resection curative; in six others with metastatic disease, the resection was considered palliative. Thus, a total of 11 of 26 patients with colorectal cancer had grossly apparent metastatic spread at the time of primary diagnosis.

Histopathologic studies showed infiltrating adenocarcinoma in 25 of the 26 patients with colorectal cancers; 11 were well differentiated, 14 moderately or poorly differentiated, and one of the latter showed carcinoid features. Four of the well-differentiated tumors were remarkable for their exuberant mucin production (Fig. 6). Of the 21 resected specimens, nine showed metastatic tumor in lymph nodes, although all had penetration of the carcinoma completely through the muscularis into serosal fat.

Four patients had extraintestinal neoplasms. These were an adenocarcinoma of the bladder, a basal cell carcinoma of the skin, Hodgkin's disease of the lymphocyte-depletion type, and diffuse histocytic lymphoma (reticulum cell sarcoma) involving lymph nodes of the right groin.

C) Clinical Features: A comparison of the clinical features in the 30 cancer patients with the overall series of 267 patients with ulcerative colitis is shown in Table I. Diarrhea and overt bleeding, seen in all the cancer patients, occurred just as frequently in the control series. Abdominal pain was also a frequent finding both in the cancer patients and in the control series, but became more severe and continuous when metastases developed. Two clinical features—abdominal mass and intestinal obstruction, both of which are relatively uncommon in uncomplicated ulcerative colitis—were found significantly more often in patients with cancer than in the control series ($p < 0.001$). In half the cancer patients, there was a long latent period of inactivity of disease, in some as long as 30 years in duration, prior to a recrudescence of symptoms at the time of development of cancer.

The site of the lesion usually determined the mode of presentation. Cancers on the right side were accompanied by weight loss, pain, anemia, and fatique, as are most right-sided carcinomas. The carcinomas of the transverse, descending, and sigmoid areas of the colon appeared most frequently with the clinical picture of obstruction. Two obstructing carcinomas, one in the descending colon and one in the sigmoid colon, were initially diagnosed radiologically as toxic dilation until barium study in one and laparotomy in the other revealed the true nature of the lesions. Two patients with infiltrating lesions had perforating carcinomas, one with massive fecal spillage. Rectal lesions predictably caused rectal bleeding and progressed to rectal stricture associated with bloody diarrhea, tenesmus, and perianal complications.

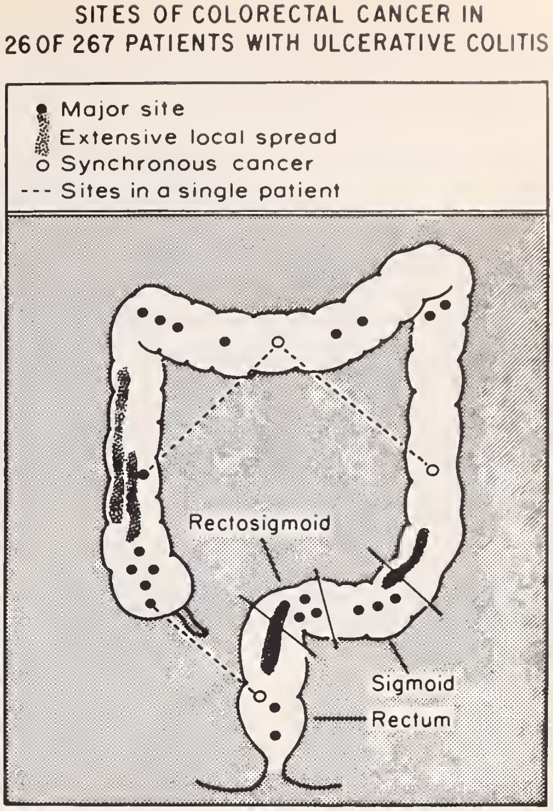

SITES OF COLORECTAL CANCER IN
26 OF 267 PATIENTS WITH ULCERATIVE COLITIS
Major site
Extensive local spread
o Synchronous cancer
--- Sites in a single patient
Rectosigmoid
Sigmoid
Rectum

FIG. 5. Sites of 29 colorectal cancers in 26 patients with ulcerative colitis.

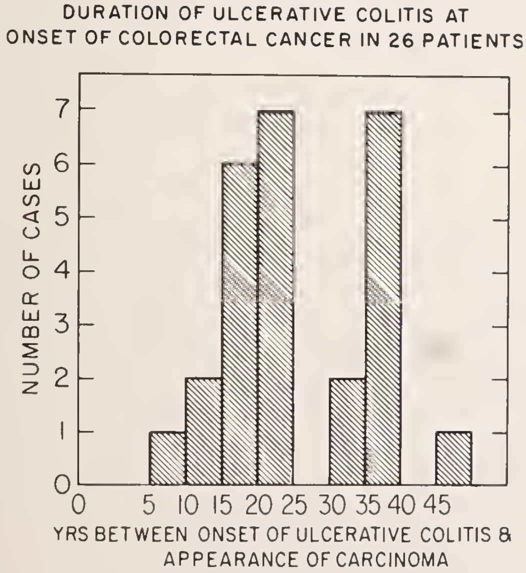


FIG. 4. Intervals between onset of ulcerative colitis and appearance of colorectal cancer in 26 patients. The mean interval is 24 years, but it was longer in left-sided than in universal disease.

D) Radiologic Features: A radiologic picture, diagnostic or highly suggestive of colorectal cancer, was found in 23 of the 26 patients with intestinal cancer. A stricture was noted in the barium enema in eight of the patients, contour defects in two patients, and ulcerating, infiltrating lesions in four. Proliferative or polypoid masses were found in nine patients, including one with a synchronous ulcerating cancer. In one patient, a complete obstruction was found in the distal transverse colon.

In two patients, the radiologic changes of advanced ulcerative colitis masked the carcinomas that were found at resection. A direct correlation could not be found between positive preoperative radiologic findings and subsequent mortality. In fact, eight long-term survivors had lesions demonstrated on preoperative barium studies: five polypoid lesions, one contour defect, one ulcerating lesion and one stricture.

E) Incidence: With data from the Third National Cancer Survey (Incidence Data Monograph 41, March 1975, DHEW Pub. #NIH 75-787, edited by Cutler, S.I. and Young, J.L., Jr.), the expected number of cancers can be calculated and a comparison made with the cancer incidence observed in this study. These comparisons are shown in Tables II-IV. In Table II, the incidence of cancer among all 267 ulcerative colitis patients is seen to

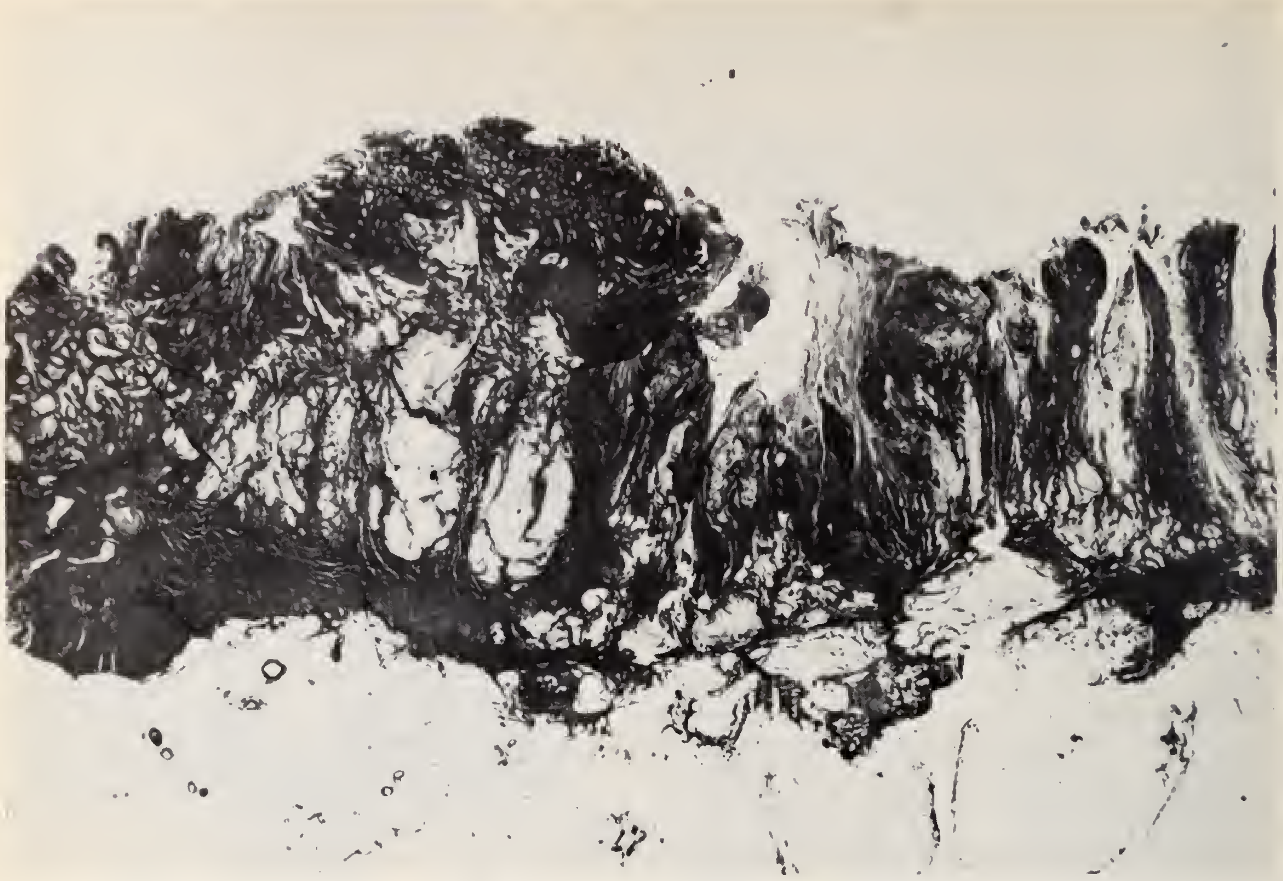


FIG. 6. Infiltrating adenocarcinoma of colon in ulcerative colitis. The tumor is well differentiated and manifests exuberant mucus production.

TABLE I

A Comparison of the Clinical Features of 30 Patients that Developed Cancer with a Control Series of 237 Ulcerative Colitis Patients

	Cancer Patients	Control Series
No. of Patients	30	237
Diarrhea	30 (100%)	228 (96%)
Overt bleeding	30 (100%)	226 (95%)
Abdominal pain	20 (67%)	184 (78%)
Peripheral systemic	15 (50%)	106 (45%)
Toxemia	13 (43%)	133 (56%)
Intestinal obstruction	13 (43%)*	16 (7%)
Abdominal mass	9 (30%)*	8 (3%)
Abdominal tenderness	9 (30%)	96 (41%)

* Significant difference from overall series ($p < 0.001$).

be eight times higher than expected. The expected (O/E) ratios occurred in the 10–19 and 20–29 year age groups. In Tables III and IV, the data are analyzed separately for universal and left-sided ulcerative colitis. The overall incidence of cancer in left-sided colitis was three times higher than expected; in universal colitis, 11 times higher. Thus, the largest discrepancy between the observed and the expected incidence of cancer occurred in younger patients with universal colitis.

F) Mortality: We obtained a 97% follow-up to 1976 or to the time of death in the 26 patients with colorectal cancer. There were 13 deaths, an overall mortality rate of 50%. Three of five cancer patients with left-sided disease (60%), and 10 of 21 with universal disease (48%), died by the time of termination of the study, compared with 7% and 6% respectively of noncancer patients (Fig. 1). Ten operated patients died of metastatic spread of the tumor, four being unresectable at the time of primary surgery. The one unoperated patient with malignant ascites died two months following diagnosis. All deaths caused by metastatic tumor spread occurred within 12 months of surgery. There were two early postoperative deaths, one from gram negative sepsis, and one following a cardiac arrest during a second operative procedure for compromised bowel. One patient died 18 months after surgery from a bleeding, perforated gastric ulcer.

Among the 13 survivors, three are alive and well nine years following resection, one at eight years, two at seven years, two at six years, two at five years, two at four years, and one at three years following surgery. This represents a mean follow-up of 6.3 years for our 13 survivors, 6.6 years for patients with universal disease, and 4.5 years for patients with left-sided disease. Figure 7 shows the postoperative survival curve of the 26 colitis patients in this series compared to that of a large reported

TABLE II

A Comparison of Age-Specific Incidence of Colorectal Cancer in Ulcerative Colitis with Expected Incidence in the General Population

Age of appearance of cancer	Standard population*	Number of cancers*	Case rate/100,000*	Patient years at risk with UC (present series)	Observed cases	Expected cases	Ratio Obs/Exp
0–9	3,847,094	4	0.10	101	0	0.001	—
10–19	4,096,825	28	0.68	396	1	0.0027	370X
20–29	3,202,946	133	4.15	608	3	0.025	119X
30–39	2,389,272	384	16.07	523	4	0.084	48X
40–49	2,554,502	1784	69.84	595	3	0.42	7X
50–59	2,155,206	4460	206.94	434	4	0.90	5X
60+	2,757,606	19805	718.20	377	11	2.71	4X
TOTALS				3034	26	3.35	8X

* Third National Cancer Survey: Incidence Data Monograph 41 March 1975. DHEW Pub. # NIH 75-787 USDHEW PHS NIH Ncl Bethesda, Md. Ed. by Cutler, S.J. and Young, J.L., Jr.

TABLE III

A Comparison of Age-Specific Incidence of Colorectal Cancer in Universal Ulcerative Colitis with Expected Incidence in the General Population

Age at appearance of cancer	Patient years follow-up	Observed cases	Expected cases*	Ratio
0–9	73	0	0.001	—
10–19	275	1	0.0019	526X
20–29	412	3	0.0171	175X
30–39	314	4	0.0505	79X
40–49	318	1	0.2221	5X
50–59	224	4	0.4635	8X
60+	226	8	1.6231	5X
TOTALS		21	1.8667	11X

* According to case rate in the standard population (see Table II).

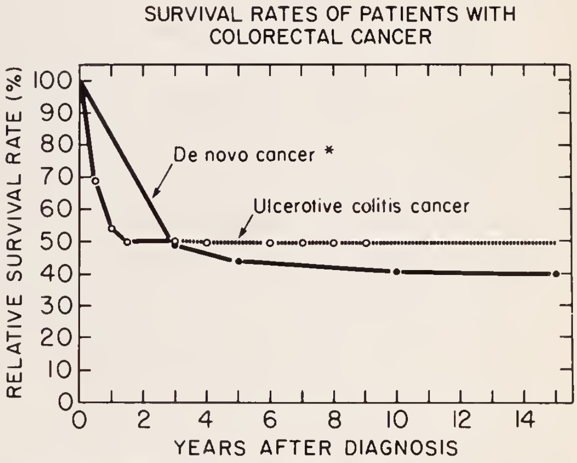
TABLE IV

A Comparison of Age-Specific Incidence of Colorectal Cancer In Left-Sided Ulcerative Colitis with Expected Incidence in the General Population

Age at appearance of cancer	Patient years follow-up	Observed cases	Expected cases*	Ratio
0–9	28	0	0.0000	—
10–19	121	0	0.0008	—
20–29	196	0	0.0081	—
30–39	209	0	0.0336	—
40–49	277	2	0.1934	10X
50–59	210	0	0.4346	–
60+	151	3	1.0845	3X
TOTALS		5	1.4864	3X

* According to case rate in the standard population (See Table III).

series of noncolitis patients developing colorectal cancer (End Results in Cancer Report No. 4, DH 1972). The three-year survival rates are similar in the two groups. Although three patients have survived nine years, the small number of patients followed for more than three years precludes any definite statement concerning long-term survival.



** Modified from "End results in cancer", report no.4, DHEW, 1972*

FIG. 7. Survival curve of 26 ulcerative colitis patients with colorectal cancer (open circles) compared with colorectal cancer patients in the general population (closed circles). Although there is an initial relatively rapid mortality among the ulcerative colitis patients, the survival curves are roughly similar after the first three years. (The "tail" of the ulcerative colitis curve is shown as a dotted line because the apparent zero mortality rate is based on experience with only 13 patients).

Discussion

Age

The mean age of 26 years at onset of ulcerative colitis in our series is consistent with that reported in previous publications. Of interest is the age-incidence curve, showing a preponderance of cases beginning in the late second, third, and sixth decades of life (Fig. 2). Acheson and others have shown that the incidence of ulcerative colitis is greatest in the third decade of life, with a secondary peak in the seventh decade (16). In the group of patients with colorectal cancer, the proportions of patients developing ulcerative colitis before age 10 (4 of 26, or 15%), and before age 20 (10 of 26, or 38%), are slightly higher than the corresponding proportions in the total series (17 of 276, or 6%, and 88 of 276, or 32%, respectively). This preponderance of younger onset cases among the cancer patients suggests either a true predisposition to the development of cancer in younger patients, or simply a longer period of follow-up in these patients. We have recently demonstrated that there was no significantly higher cancer incidence in those patients with childhood onset of colitis, independent of their customarily longer durations of follow-up (17).

The mean age of 51 years at onset of carcinoma is virtually the same as the 50 years reported by Cook and Goligher, but somewhat greater than the 42.5 years reported by Slaney and Brooke (7, 18). In any event, the mean age at onset of carcinoma in this series is at least 10 years younger than the age of onset of colorectal cancer in the general population (19, 20). Consequently, the proportions of our patients developing cancer below the age of 40 (27%), and below the age of 50 (46%), are substantially greater than the 4.4% and 14%, respectively, reported by Dwight et al, for de novo rectal cancer (19). These figures all agree with previous observations that colorectal cancers develop earlier in patients with ulcerative colitis than in the general population (10, 13).

It is important to note that five of the 26 patients with colorectal cancer had left-sided rather than universal disease. Although there is a suggestion from our data that it may take longer for cancer to develop in left-sided than in universal disease (mean, 32 vs. 23 years), the fact remains that universal disease is evidently not a prerequisite to the development of cancer.

Site

It appears that the location of carcinomas in ulcerative colitis differs from the noncolitis population. Mottet, who reviewed nine separate series with a total of 38% carcinomas secondary to ulcerative colitis, noted that the rectum and sigmoid were involved in 45% of cases (21). This proportion is similar to that in our series, 11 of 29 cancers (38%). Goldgraber and Kirsner found an even lower proportion (27%) of rectosigmoid carcinomas in patients with ulcerative colitis (13). The important point is that all these percentages for rectosigmoid location of colon cancer in ulcerative colitis patients are substantially lower than those for the general noncolitis population. Four separate large series of colorectal cancers in the general population indicate that the proportion of colon cancers located within the rectosigmoid area is in the range of 68% to 70% (22–25). Furthermore, in the series from the general population, cancers were relatively uncommon in the transverse colon, occurring in 6% of cases, while in our ulcerative colitis series the proportion in the transverse colon was 24%. Similarly, the proportions of cancers in the ascending colon and cecum in the general population series was 15%, as against 24% in our series. All of these figures seem to indicate an increased predilection of colorectal cancer for the proximal colon in patients with colitis.

The relatively high incidence of multiple cancers in 12% (3 of 26) of our patients is in keeping with the 14%–42% frequency reported in several previous series (7, 10, 13, 17, 26). The incidence of multiple cancers in ulcerative colitis patients is much more than the 2%–3% reported for colorectal cancer in the general population (27).

Clinical and Radiologic Features

Goligher et al stress the "difficulty in diagnosing concomitant cancer" at an early stage in ulcerative colitis (11). They and other authors failed to make an early diagnosis in half their patients (1, 2). Although the diagnosis was made preoperatively in most of our patients, it was still too late for many, as indicated by the metastatic stage of 42% (11 of 28) of the cases, and by the 50% mortality at 18 months.

A frequent clue to the diagnosis of cancer was the presence of stricture in 27% (7 of 26) of our patients. This incidence is similar to the 23% reported by Hinton from St. Mark's Hospital, and the association of carcinoma with stricture in ulcerative colitis has been reported frequently by others as well (3, 7, 10). The cancers were undetected by barium enema in two of our cases. The use of colonoscopy may provide additional help in the recognition of such occult lesions.

There are other signs besides x-ray findings that should alert the physician to the possibility of colorectal cancer. These include the development of symptoms following a long period of quiescent colitis, a feature noted in half our cases. The development of intestinal obstruction or palpable abdominal mass in ulcerative colitis is also suggestive of cancer, as these two symptoms were observed significantly more often ($p < 0.001$) in the cancer group than in the overall series of colitis patients (Table I).

Incidence

Ours is a selected referral series of hospitalized patients, whose incidence of cancer could not be expected to be typical of the incidence of cancer among all patients with ulcerative colitis. Nevertheless, the 9.7% occurrence (26 of 267) of adenocarcinoma of the colon that we have found in this series is similar to the 11% reported by Counsell and Dukes from St. Marks Hospital in London, another major referral center for large bowel disease (1). Indeed, our figure falls within the higher part of the range previously reported, which extends from 0% to 14.2% (8, 28).

The ratio of observed to expected cancer incidence (O/E ratio) in this series, compared to a standard population, was 8 times higher. This figure is compatible with the 11-fold increase in colorectal fatality rate reported by Goligher et al, although it is less than both the 20-fold increase reported by Bargen et al, and the 25-fold increase recently noted by Lennard Jones et al (11, 14, 29). There are two principal reasons for our relatively lower O/E ratio. The first reason is that we have calculated cancer incidence in our ulcerative colitis patients on the basis of patient years of follow-up from onset of disease, while others have calculated the incidence on the basis of patient years of follow-up from first documentation at the study center (9, 29). The second reason for our lower O/E ratio is that we have calculated the expected incidence (E) on the basis of the latest National Cancer Survey (1975), which has shown a much higher incidence in the general population than previous surveys such as the Connecticut Tumor Registry (Cancer in Connecticut. (1963) Connecticut State Department of Health, Franklin M. Foote, Commissioner, Hartford, Connecticut).

We have noted a progressive rise in the O/E ratio among progressively younger patients in this series. This observation simply reflects the fact that colorectal cancer is exceedingly rare in young people in the general noncolitis population, so that even a low cancer incidence among our young colitis patients will yield a high O/E ratio. However, within the ulcerative colitis population itself, early age at onset of colitis does not appear to exert any independent influence on cancer risk, except for being conducive to a longer duration of disease (17).

Mortality

In the referral series, there was a 50% mortality within eighteen months of diagnosis of carcinoma (Fig. 7). Truelove and Pena have shown a higher mortality and more severe disease in referred patients with Crohn's disease, and their findings are probably relevant to all forms of inflammatory bowel disease (30).

The ten patients (38%) that have survived five years or longer following surgery exceed both the 25% 5 year survivors that were reported by Cook and Goligher and the 18% that were reported from a survey of 9000 cases in the literature by Slaney and Brooke (7, 18). Our figure is similar, however, to the 36% reported by Goldgraber and Kirsner and the 40% by Hinton (3, 13). In any event, it would seem from this series that the 5-year survival rate with colorectal carcinoma in ulcerative colitis is only slightly less than the 50% observed in colorectal carcinoma arising de novo (15, 20, 22). Perhaps this favorable survival experience is a result of the high proportion (44%) of well-differentiated cancers in this series, since Hinton has noted that the poorer prognosis of colitis-related cancer is correlated with a higher proportion of anaplastic tumors (31). Hughes et al recently reported that the survival curve derived from colitis-cancer patients was almost identical to that of age-matched controls (32). Our survival curve (Fig. 7), with 50% of patients alive at three years and no deaths thereafter, supports their contention that early radical surgery can result in survival similar to that of noncolitis colorectal cancer.

In other words, while there is a considerable early mortality, resulting from difficulty in making an early diagnosis in these patients, there is, conversely, a substantial long-term survival in patients who survive the first 18 months. All 13 of our patients that survived the first 18 months are still alive today, with a mean follow-up of 6.3 years (range 3–9 years). Indeed, of the 15 patients with no grossly obvious metastatic spread at the time of laparotomy, only two have died, both from immediate postoperative complications, and all but one of the 13 survivors are still cancer free. The prospect of improving long-term survival with earlier detection and treatment therefore makes effective cancer surveillance for ulcerative colitis patients an important practical goal.

Summary

Cancer developed in 30 of 267 ulcerative colitis patients admitted to The Mount Sinai Hospital between 1960 and 1976. There were 26 patients with 29 colorectal cancers, and four patients with extraintestinal cancers. Colorectal cancers in this series were more often multiple and more proximal in distribution than colon cancers in the noncolitis population. Signs specifically associated with colorectal cancer included a palpable abdominal mass, intestinal stricture and obstruction, and late recrudescence of symptoms.

Twenty-one of the 26 patients with colorectal cancer had universal colitis and five had left-sided disease. Compared to a standard population, the observed-to-expected (O/E) ratio of colorectal cancer incidence among all our ulcerative colitis patients was eight, with the ratio being 11 in universal colitis and three in left-sided disease. It is important to recognize that after a sufficiently long interval, cancer may develop in left-sided as well as in universal ulcerative colitis.

The mortality from colorectal cancer was 50% at 18 months, with ten of 13 deaths due to metastases. There were ten (38%) five-year survivors. Long-term survival was not limited to patients with subclinical cancers, since eight of the nine 5-year survivors studied by barium enema had positive radiologic findings preoperatively. The long-term mortality from colitis-associated cancer did not appear to be worse than that from colorectal cancer in the general population.

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To See or Not to See: The Status of the Autopsy at The Mount Sinai Medical Center

STEPHEN A. GELLER, M.D.

Introduction

Approximately 200 years ago, it became increasingly apparent to concerned physicians that the lessons learned at the bedside were not sufficient and that the understanding of diseases required the study of the patient after death as well. Medical practitioners determined that recognizing the morphologic basis of disease could allow greater accuracy in making diagnoses during life. In addition, the autopsy seemed to offer a means for evaluating the efficacy, or lack thereof, of treatment. Certain physicians were able to combine the special skills and knowledge of the autopsy room with their own bedside observations to such effect that the lessons taught by Morgagni, Bichât, Laennec, Hodgkin, and countless others are still being learned today.

In the last half of the 19th century, the magnificent Viennese tradition of pathology was established by one of the greatest descriptive morphologists, Rokitansky. His brilliant clinicopathologic correlations and his commitment to the autopsy as a major endeavor established the pattern of the practice of pathology. Rudolf Virchow combined clinical expertise and devotion to the autopsy with techniques of microscopy. Virchow formulated the still valid concepts of the cellular basis of disease. In so doing, he also indelibly defined pathology as a unique discipline of medicine and the pathologist as the specialist best able to interpret morphologic alterations as they reflect clinical events. The utility of the autopsy became universally recognized after the 1858 publication of Virchow's "Cellularpathologie" although the concept had been firmly established by Morgagni's "De sedibus et causis morborum" more than a century before.

In the first half of the 20th century, one of the greatest figures of medicine was Paul Klemperer, a pupil of Rokitansky's student, Sternberg. Klemperer served as Pathologist to The Mount Sinai Hospital for more than a quarter century. He considered himself to be primarily a teacher of physicians and utilized the autopsy as the best means of understanding the natural history of disease. Klemperer and his successor, Hans Popper, brought the lessons of the Viennese tradition to Mount Sinai and were masters of the clinicopathologic correlation. Under their leadership, the autopsy flourished as a major component of the practice of medicine at The Mount Sinai Hospital. Questions arising from observations at the autopsy table became the impetus for investigation and experimentation.

In spite of this tradition, fewer autopsies were performed at The Mount Sinai Hospital in 1977 than in any year since 1920. In general, the number of autopsies has steadily declined in recent years, whereas the number of deaths has risen or remained stable (Fig. 1). The decline of the autopsy is certainly not limited to Mount Sinai, although the implications at this institution may be more serious than at some others (1–7). It is appropriate, therefore, to identify some of the reasons for the decrease in utilization of the autopsy and, in so doing, to attempt to find solutions.

Stated reasons for the Decline of the Autopsy

Diagnoses are usually established during life. Technologic advances have provided highly sophisticated, noninvasive methods for establishing diagnoses. In spite of these advances, factors contributing to death may defy recognition as much as 50% of the time (8–10). The major clinical diagnosis itself may be incorrect in as many as 40% of autopsied patients (10–19). During the calendar year 1976, 395 autopsies were performed at The Mount Sinai Hospital, 340 involving adults. Major discrepancies between the autopsy and clinical diagnoses were documented in 15% of the adult cases. This is relatively better than the situation at many institutions. However, it is relevant to note that approximately 800 patients dying at Mount Sinai in 1976 were not autopsied. There are no data regarding our selection criteria for autopsies. Gall

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From the Department of Pathology, The Mount Sinai Medical Center, New York, N. Y. 10029

Requests for reprints should be sent: Dr. Stephen A. Geller, Department of Pathology, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, N. Y. 10029

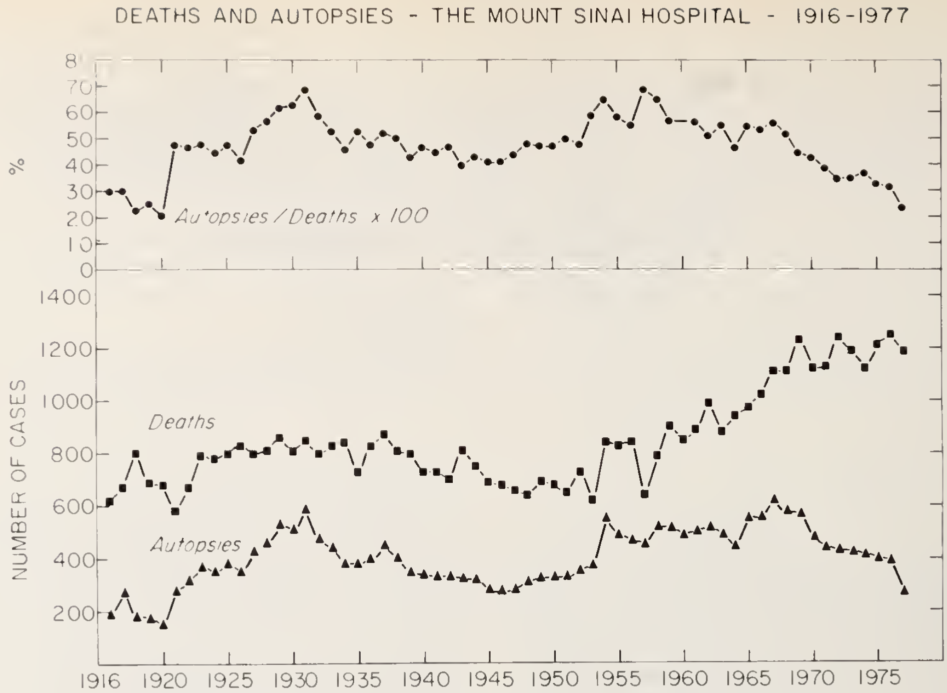

FIG. 1.

has documented the remarkable similarity of the percentage of errors in diagnoses, disclosed by autopsies, at two major institutions over a period of 50 years (20). However, the use of the autopsy in 1978 is not to correct diagnoses, but to further understand the natural history of disease and a patient's response to therapy.

Nothing new is learned from the autopsy. The autopsy has, in recent years, aided in the recognition of a variety of new diseases and conditions, and has been a particularly effective tool for refining our knowledge of well-established entities (20). The list of recent entities that have become better understood on the basis of postmortem studies is extremely long. It includes such diverse conditions as idiopathic hypertrophic subaortic stenosis (IHSS), asbestosis, mesothelioma, pneumocystosis and other opportunistic infections, iatrogenic cardiomyopathies, nonbacterial thrombotic endocardiosis (NBTE), adult respiratory distress syndrome, disseminated intravascular coagulopathy (DIC), angioimmunoblastic lymphadenopathy, and multifocal leucoencephalopathy. There has been new understanding of the morphogenesis and pathogenesis of cirrhosis, appreciation of the changing spectrum of endocarditis, and recognition of the relationship of coronary thrombosis to myocardial infarction. The autopsy is of inestimable value in studying the etiology of the current major causes of death and in accumulating evidence about the importance of environmental factors in the pathogenesis of these diseases. Modern research methods have been adapted to the autopsy and are providing new insights into the subcellular phenomena that occur in injured and dying cells (22, 23). Our awareness of occupationally and environmentally induced disease has stimulated renewed interest in large scale autopsy studies of affected groups as the best way to measure and understand the pathogenesis and complications of a wide range of conditions (24). The autopsy serves as an index of the efficacy of our therapeutic activities, surgical and medical. It also allows evaluation of the effectiveness and the toxic effects of modern drugs (25).

The autopsy does not always solve clinical problems. If this statement were amended to "morphology does not always solve clinical problems" there would be little argument. An anatomic basis for death is not found at every autopsy. However, the autopsy is not an anatomic exercise. The well-planned and well-performed autopsy is a demonstration of clinicomorphologic relationships. It is rare that the autopsy fails to contribute to the understanding of the clinical events. Indeed, the death certificate, completed by the clinician without benefit of the autopsy findings, is frequently in error. Thus, a considerable portion of the data used for studies of disease patterns may be incorrect (12, 19). Of 43,790 deaths in Finland in 1967, only 103 (0.23%) were analyzed as obscure after a forensic autopsy (26). Wilens has whimsically commented on the continuing problem of the pathologist who identifies a plethora of clinically relevant morphologic alterations and yet fails to satisfy the clinician's queries (27).

The family objects to the autopsy on religious grounds. There is no Christian law or papal writing, that forbids human dissection (28). Not only were a number of popes themselves autopsied, but a bill was issued in the 15th century by Pope Sixtus IV (29) permitting studies on human bodies by the students at Bologna and Padua. In contrast, the laws of Judaism maintained strict restrictions against the autopsy until modern times (29, 30). In strict interpretation, autopsy could only be permitted to save the life of a patient immediately at hand, and not, as was often misinterpreted, some problematic future patient. In modern times the problem of the autopsy has been dealt with by an agreement between the Chief Rabbinate of Israel and the Hadassah University Hospital in Jerusalem (31). Under the terms of this agreement, the Chief Rabbinate does not interfere with autopsies in four categories: 1) autopsies required by law to determine if foul play has occurred; 2) cases in which the physician cannot ascribe the cause of death to a particular disease without an autopsy; 3) cases in which an autopsy may help another patient at the time; and 4) hereditary disease cases in which the autopsy may be invaluable in guiding the family. The modern interpretation allows for autopsy even in cases involving the most orthodox. A religious proscription against autopsy is rarely a determining factor in failing to obtain permission if the autopsy is medically indicated.

It takes too long to get the results. This is true! The techniques for processing tissues and the criteria for diagnosis are the same for autopsy pathology as for surgical pathology. Interpretations on surgical specimens submitted for diagnosis are routinely rendered within 24 to 48 hours of excision; whereas, even under the best of circumstances, an autopsy report may not be prepared for three to four weeks. Clinical demands on a hospital require sufficient professional, technical, and paraprofessional staff to allow for rapid interpretation of tissues removed during life. Surgical pathology is an area with major clinical responsibility and has priority in any department providing diagnostic service. It is to be noted that clinicians do not demand a similar response for autopsy. Consequently, delays in processing and completing autopsies are often occasioned by limitations of technicians and secretaries whose prime responsibility is to the surgical pathology area. The complete autopsy must include a mechanism for immediate communication of preliminary findings. In most cases, with adequate technical and secretarial support, final interpretations could be provided in less than two weeks. The delivery of an expeditiously completed autopsy report is basic if the autopsy is to again become a vital part of the clinical course. This is only part of the answer, however. The autopsy has become less important in the modern pathologist's life. Clinical laboratories, surgical pathology, and cytopathology require major and immediate attention by the pathologist, both in terms of patient care and financial realities.

Physicians today are too busy to visit the autopsy room. Pathologists must recognize that most clinicians do not visit the autopsy room. This is the product of many factors: deemphasis of pathology in medical school curricula, misconceptions about the accuracy of premortem diagnoses, and, not least of all, a paucity of pathologists with clinical experience equivalent to that of practicing physicians. Perhaps the most significant factor has been the changing attitude of pathologists themselves (32).

As cellular biology became more and more a part of the pathologist's interest, the autopsy became less. The autopsy is often left to the least experienced member of the department as the senior members become involved with more sophisticated scientific endeavors. The autopsy is time-consuming and does not contribute to the earning power of the clinical laboratory. In the teaching institution the autopsy cannot compete either with surgical pathology or research activities as a basis for professional and academic recognition or advancement. Angrist has noted that "if mere publication is equated with creative scholarship, the autopsy cannot compete" (33). The loss of academic prestige of the autopsy contributes to its further decline. Senior pathologists seek other avenues of academic expression and, in turn, become unavailable for immediate consultation with clinicians who require autopsy interpretations at or near the time of death. Consequently, there is little motivation for the busy clinician to visit the autopsy room. The junior pathologist is then deprived of the opportunity for meaningful discussion of clinical problems and may have little incentive for the importance of the time-consuming and occasionally difficult postmortem examination. The unsatisfactory situation is further compounded when an autopsy technician, rather than a physician, performs the autopsy. The trend to relying on autopsy technicians is rather shortsighted. If the autopsy is to remain a meaningful segment of the clinical course it will require more rather than less of the pathologist's time and interest. The autopsy technician can prove to be useful as the pathologist's assistant, rather than replacement, to facilitate special techniques that enhance the teaching value of the dissection.

The autopsy results may lend support to a malpractice suit. Fear of embarrassment and/or litigation occasionally may contribute to failure to obtain permission for autopsy at some hospitals. This is probably not a frequent occurrence at a teaching institution. Thorough postmortem examination may support the defense of a physician that has delivered adequate medical care. Indeed the absence of an autopsy may lend a question of uncertainty in a suit involving a patient that has died. There are almost no data in regard to this question and opinions must prevail. Documented instances where the performance of an autopsy has been a major factor in a malpractice suit are exceedingly rare.

The family doesn't want the body mutilated. The autopsy is not a mutilating procedure and incisions are limited to the parts of the body usually covered by clothes. Clinicians that are unfamiliar with the procedures of autopsy are also unable to respond adequately to this fear. Thus, they either fail to obtain permission for autopsy or they limit the extent of autopsy. The limited autopsy is often unsatisfactory and contributes greatly to the impression that "the autopsy doesn't solve clinical problems." We could list many cases to illustrate this: the patient with localizing cerebral signs but permission for brain examination not granted; the patient with hypercalcemia but permission limited to abdominal examination only; the patient with interstitial pulmonary fibrosis possibly related to Bleomycin therapy but permission limited to a sample of abdominal tumor; the patient with postoperative liver failure but permission limited to examination of thoracic incision.

Families are less willing to give autopsy permission than they used to be. Although data to support or refute this contention are sparse, there is considerable reason to doubt its validity. The critical factor in obtaining permission for autopsy is the physician—not the family. Katz and Gardner have investigated the factors affecting permission for an autopsy (34). They concluded that a hospital's autopsy rate is not determined by the sociocultural religious character of the patient population. Outside interest in the autopsy may exert a positive influence on house staff motivation for obtaining autopsy permission. Additional exposure to the problem of death, during medical school and house staff years, is needed. Another documented factor in determining whether or not an autopsy is permitted is age, both of the deceased and the next of kin (35). Autopsy permission is less often sought, and when sought, less often granted, with increasing age of deceased or next of kin. In spite of familial reluctance, the physician should recognize that the autopsy itself may provide considerable emotional support for the family (36). Guilt feelings may be allayed and comfort provided with a full understanding of the death. Encouragement and a sense of fulfillment may follow the knowledge that a kidney or a cornea will be given to a living patient. The clear definition of death may affect the application of insurance benefits. The family may immediately benefit, of course, in cases of genetic or contagious diseases. However, the family can only benefit from the autopsy by learning the results of the autopsy. The physician must recognize that responsibility does not end with death. Family conferences should be the last stage in the care of the patient who has died. This will require excellent communication between pathologist and clinician and, subsequently, between clinician and family. Family members who have not had a supportive and educative experience with an autopsy may dissuade others from granting permission for autopsy (36).

The Role of the Autopsy

Many of the contributions of the autopsy to the modern practice of medicine have been discussed, others will now be briefly reviewed.

Quality control in medical care. The concept of quality control has been well developed in the clinical laboratory and might be defined simply as the procedures necessary to guarantee the reliability of tests. Recent trends in formalizing the concepts of peer review are clearly designed to assure quality control in the practice of medicine. The autopsy is the "ultimate control in the self-appraisal of a doctor's diagnostic and therapeutic ability" (7). Today, the autopsy can serve as the monitor of the excellence of medical care and may be the most vital part of medical care evaluation studies (33, 37–40). Indeed, the autopsy, if utilized appropriately, could serve as the basis for objective decisions on the cost-effective use of hospital facilities (40). The autopsy is the single most reliable means of confirming, clarifying, and correcting diagnoses, determining the accuracy and applicability of new diagnostic modalities, of evaluating the efficacy and complications of new forms of therapy, and gauging the quality of surgical procedures.

Medical education. The potential of the autopsy to provide meaningful and stimulating undergraduate educational experiences cannot be exaggerated, both in terms of clinicopathologic correlations and in emphasizing the relevance and vitality of anatomy (41–43). The possibilities for graduate medical education are less formal but no less significant (20). In this regard, quality control and research become inseparable. Of critical importance, although only rarely discussed, is the vital role of the autopsy as the only means to provide residents in pathology with the firm basis for rendering diagnoses in surgical pathology, that is, diagnoses on living patients (44). There should be no distinction between surgical pathology and autopsy pathology; they complement each other.

Law enforcement. The traditional applications of the autopsy to law enforcement are well recognized in terms of violent crimes. In recent years, however, the scope of the forensic pathologist has been broadened to include various aspects of environmentally and industrially induced conditions (45, 46).

Benefits to society. It is beyond the scope of this discussion to comment extensively on the potential benefits that society at large may derive from well-performed and well-documented autopsy studies. We might, however, mention 1) biomedical research, 2) tissues for transplantation, 3) pharmacologic extracts (47), 4) accumulation and interpretation of accurate vital statistics, 5) epidemiology of diseases, 6) identification of injurious environmental agents and their effects, 7) documentation of harmful effects of therapeutic agents, and 8) recognition of morphologic alterations as precursors to malignancy.

Recommendations

The pathologist is the key to reversing the decline of the autopsy. That reversal will require renewed understanding by pathologists and clinicians of the critical role the autopsy can play in health care. Hospital administration must be helped to understand the major service the autopsy should provide for the evaluation of the cost-effectiveness of hospital activities as well as for the maintenance of excellence in medical care (48). Newer approaches to the information-handling aspects of the autopsy may be useful in improving the quality of communications relating to the autopsy, but they cannot provide a remedy for the pathologist's failure to fulfill a dynamic role (49–52). Senior pathologists again must develop and demonstrate skills in the performance of autopsies and must utilize modern techniques to document clinicopathologic correlations. Communication of the results of autopsy to clinicians must be prompt and, equally important, intelligible. Teaching conferences must provide the critical findings of gross and microscopic examination as well as the results of more sophisticated studies, soon after the patient's death for the autopsy to persist effectively as part of the complete clinical evaluation. Adequate technical and clerical support must be provided to make this possible. The pathologist must emphasize and reemphasize the importance of every case not only in terms of the cause of death, but as a basis for the continuous monitoring of the quality of medical care. In addition, every autopsy must be regarded by pathologist and clinician alike as a research activity (53). Newer methods must be developed for the further understanding of well-recognized disorders and for the recognition of new conditions. Trained dieners and autopsy technicians must be available to assist with the autopsy, in particular, with the ancillary techniques such as injection studies, radiography, whole organ sections, tissue preservation and culturing, and photography that enhance the research and educational value of the autopsy (54). Clinicians must be taught anew, by the pathologist, to appreciate better the value of the autopsy and, subsequently, to demand as much from the autopsy pathologist as from any other practitioner of medicine. The autopsy should be fully utilized in undergraduate and graduate education. Thus, there must be sufficient numbers of competent and committed pathologists on staff to allow for these educational activities. In this regard the pathologist should virtually be exploited and clinicopathologic confrontations should be as much a part of the daily life of the hospital as clinical rounds. The autopsy pathologist's contributions must be of the highest quality. The institution must be prepared to recognize this quality and contribution and must provide rewards—both academic and financial—for excellence in service, teaching, and research as they relate to the autopsy. Recently, there has been formal recognition that the autopsy costs money and that mechanisms should be developed to support quality autopsies (55–58). Finally, the pathologist cannot wait for the autopsy to be rescued by clinicians, administrators, demographers, public health officials, students, or any of the many groups that stand to benefit from the autopsy. The autopsy is a unique contribution pathology can make to the practice of medicine. It is the responsibility and privilege of the pathologist to maintain and improve the autopsy and to actively demonstrate its enormous and continuing value.

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Angioimmunoblastic Lymphadenopathy: Termination as Diffuse Lymphosarcoma with Plasmacytoid Features

A. OLUSEGUN FAYEMI, M.D., MAJID ALI, M.D., EVALYNNE V. BRAUN, M.D., AND
THOMAS DECECIO, M.D.

Abstract

The evolution of angioimmunoblastic lymphadenopathy (AILD) to a malignant lymphoma with plasmacytic features in a 77-year-old woman is presented. The transition occurred within one month. Other previously reported cases of malignant transformation in AILD are reviewed. The high mortality rate and the diffuse organ involvement characteristically found in AILD would suggest that the disorder is neoplastic ab initio.

Introduction

Angioimmunoblastic lymphadenopathy (AILD), recently delineated as a distinct clinicopathologic entity, is characterized by partial or complete obliteration of lymph node architecture, diffuse proliferation of endothelial cells and small blood vessels disposed in a plexiform or arborizing pattern, nodal infiltration by transformed lymphocytes with plasmacytoid features (immunoblasts), and irregular interstitial amorphous eosinophilic deposits (1–3). The patients are usually elderly and complain of fever, night sweats, weight loss, skin rash, pruritus, and generalized lymphadenopathy. Hepatomegaly is typical. Most patients have hypergammaglobulinemia with a polyclonal pattern on electrophoresis; some have Coombs' positive hemolytic anemia and others have leucocytosis.

The clinical course in AILD is notoriously unpredictable. Some cases have evolved into malignant lymphomas of different histologic types (3–9). We recently encountered a patient with AILD who subsequently developed a diffuse lymphoplasmalytic proliferation disease indistinguishable from a malignant lymphoma. The present report describes the clinical and pathologic features of the disease in this patient.

Case Report

A 77-year-old white woman was admitted to Holy Name Hospital with fever and lymph node enlargement. Bronchopneumonia, treated with vibramycin, was diagnosed a few weeks prior to admission. She had an uneventful recovery. Additional symptoms at the time of admission were anorexia, weakness, and generalized aches and pain.

Physical examination revealed bilateral cervical lymph node enlargement; some nodes were matted and slightly tender. The axillary and inguinal lymph nodes were also enlarged. The abdomen was soft and the liver was enlarged. The spleen was not palpable. There was an itchy maculopapular rash most prominent on the trunk and lower extremities.

At admission, blood pressure was 150/90, temperature 102° F, BUN 14 mg/dl, total proteins 7.0 gm/dl with albumin 2.65 gm/dl, and gamma globulin 2.33 gm/dl. Protein electrophoresis showed polyclonal gammopathy. Platelet count was 75,000/ml, white blood cells 6,000, with 73% polymorphonuclear, 12 bands, 14 lymphocytes and 1 eosinophil. Coombs' and VDRL tests were positive. Rheumatoid factor was present. The blood culture was negative on numerous occasions.

Lymph node and skin biopsies were performed. On the basis of the diagnosis of AILD, she was treated with prednisone and supportive medications. Her fever diminished, the lymph nodes decreased in size, and the rash faded. She was discharged one month after admission.

The patient was readmitted about three weeks later with fever, cough, dyspnea, and severe prostration of four days' duration. Physical examination revealed bilateral basal inspiratory rales. There was bilateral dullness of the posterior chest on percussion. The abdomen was slightly distended and the liver was palpable but nontender. Other organ systems were unremarkable. The follow-

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From the Departments of Pathology and Medicine, Holy Name Hospital, Teaneck, N. J. 07666.

Requests for reprints should be sent to: A. O. Fayemi, M.D., Department of Pathology, Holy Name Hospital, Teaneck, N. J. 07666.

ing laboratory data were obtained at admission: hemoglobin 10.3 gm/dl, white blood count 8100 with normal differential, normal electrolytes, and BUN. Blood cultures were negative. The hospital course was marked by increasing dyspnea, intermittent afebrile periods, increasing peripheral lymphadenopathy and intense cutaneous rash. Supportive therapy that was instituted consisted of antibiotics, intravenous administration, adrenocortical steroids and oxygen. The patient's condition progressively deteriorated. She responded poorly and expired one month after admission.

Pathology: Lymph node biopsy

The lymph node measured 5.5 cm in maximum dimension, was moderately firm, and revealed a homogeneous gray appearance on cut section.

Microscopically, the nodal architecture was partially effaced by proliferating mononuclear cells and arborizing small vessels. The walls of the vessels were thickened and cellular. In areas, prominent endothelial proliferation was evident. The cellular proliferation consisted of plasmacytoid cells, plasma cells, and immunoblasts. A mild degree of atypia was present. There was capsular invasion with involvement of perinodal fatty tissue, most prominent at the hilus of the lymph node. Eosinophilic leucocytes were encountered occasionally. Focal interstitial accumulation of homogenous eosinophilic material was seen. The histologic appearance was characteristic of angioimmunoblastic lymphadenopathy (Fig. 1).

Postmortem Findings

There was generalized lymph node enlargement most prominently in the cervical, axillary, mediastinal, periportal, peripancreatic and paraaortic regions (Fig. 2). The largest lymph nodes measured up to 4 cm in maximum dimension and in many areas were matted. They were moderately firm and fleshy. Focal necrosis was present in some. Microscopically there was complete effacement of the lymph node architecture by mature tumor cells and by immature lymphoid and plasmacytic cells (Figs 3, 4). Atypical forms commonly were seen. Mitoses, many atypical, were rampant. There was capsular infiltration with extensive perinodal invasion. Large anaplastic cells of the type usually seen in immunoblastic sarcoma were absent. The morphology was that of a diffuse malignant lymphoma.

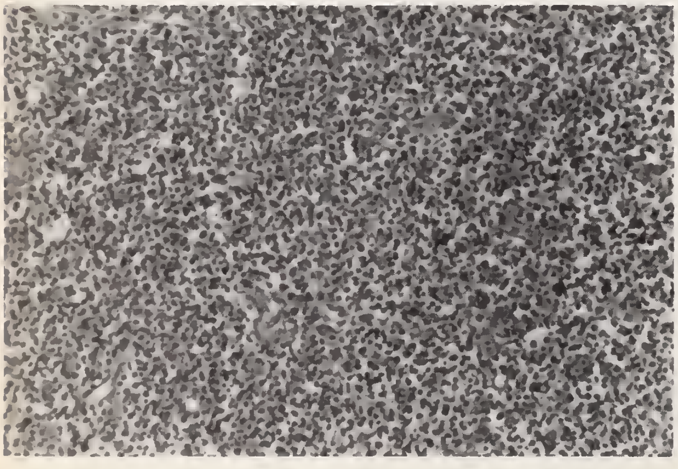

Fig. 1: Lymph node showing angioimmunoblastic lymphadenopathy (AILD). The characteristic plexiform vascular proliferation and obliteration of architecture are evident (H&E, × 100).

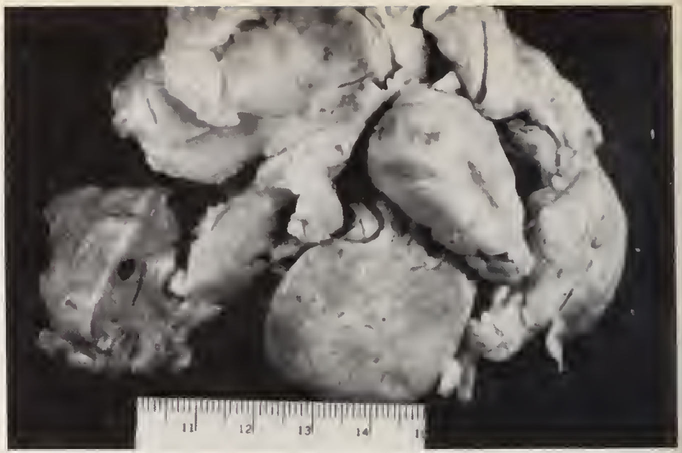

Fig. 2: Gross photograph of lymph nodes showing prominent enlargement and matting together, evidence for malignant transformation.

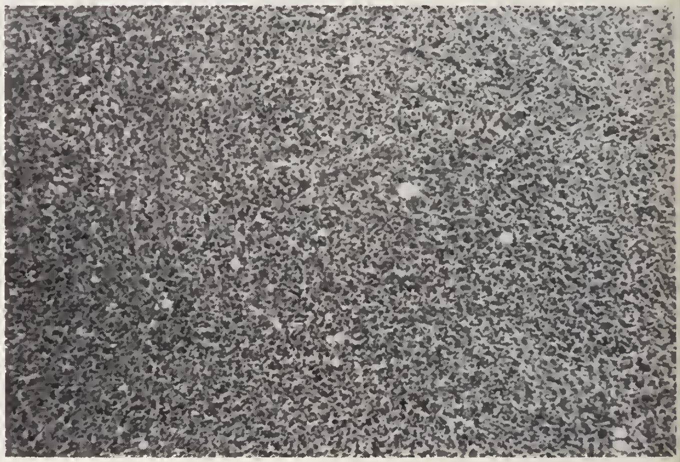

Fig. 3: Diffuse destruction of lymph node by malignant lymphoma. Vascular proliferation is less pronounced (H&E, × 40).

The liver weighed 1350 gm and showed an accentuated lobular pattern with focal minute nodular infiltration. The portal tracts, hepatic lobules and sinusoids contained tumor infiltrate whose composition was similar to that found in the lymph nodes (Fig. 5). The spleen weighed 450 gm and showed a recent infarct and focal neoplastic infiltrate. Both lungs weighed 950 gm. They revealed bronchopneumonia and neoplastic infiltration of blood vessel walls, bronchi and alveolar septa (Fig. 6). A postmortem lung culture in consolidated areas yielded Hemophilus influenzae. Neoplastic infiltrate was present in the skin, bone marrow, kidneys, and esophagus.

Discussion

Since 1974 when Frizerra et al, first defined AILD as a clinicopathologic entity, two large series and numerous case reports have appeared in the literature (1). The clinical and pathologic features of this disease are well known. Disappointingly, however, the clinical course and outcome of AILD cannot be predicted from either the clinical manifestations or the histologic appearances of the lymph nodes. The prevailing opinion as to the nature of AILD regards it as nonneoplastic. This conclusion has been based predominantly on the morphologic features such as the lack of atypia of the proliferating cells, the absence of visceral masses at postmortem examination of fatal cases, and the noninfiltrative pattern of cellular infiltrate when extranodal organs are invovled (1–3). Despite the partial to complete obliteration of nodal architecture, the peripheral sinuses of the lymph nodes remain open and remnants of germinal centers may be present (1, 2, 10). Moreover, the end stage of AILD is manifested as lymphocytic depletion and perivascular fibrosis of involved organs (10). Some patients recover completely from the disease regardless of treatment. This seems to corroborate the benignity of AILD.

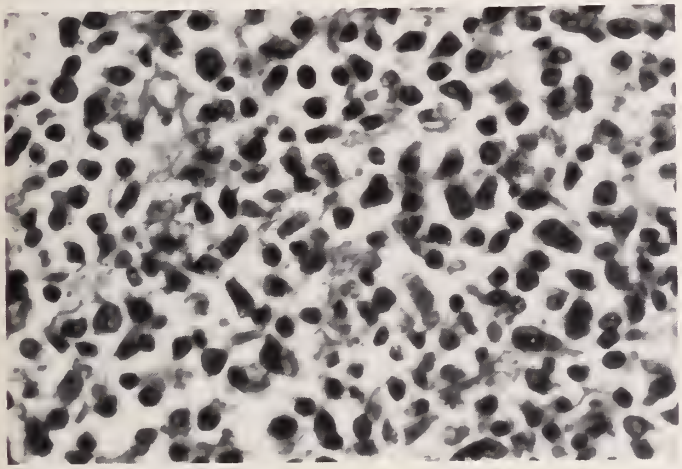

Fig. 4: High power detail showing atypical lymphoid cells with plasmacytic differentiation. Some of the neoplastic cells show vesicular nuclei and conspicuous nucleoli (H&E, × 400).

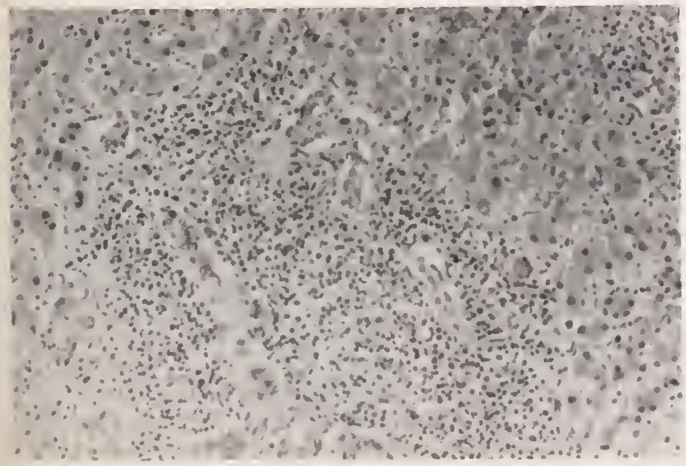

Fig. 5: Enlargement and infiltration of portal tracts by neoplastic infiltrate. Focal intralobular infiltrate is also present (H&E, × 100).

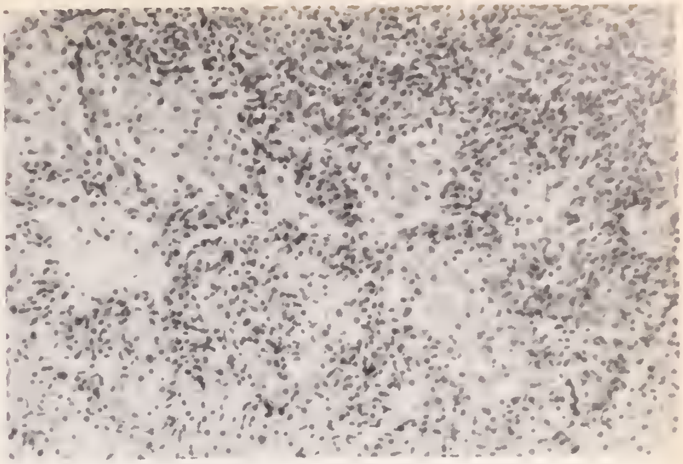

Fig. 6: Thickening of pulmonary alveolar septa by malignant lymphoma (H&E, × 100).

More recently the possibility that AILD is a neoplasm of the lymphoreticular system has been raised. Twoney drew an interesting analogy between AILD and Hodgkin's disease (22). Features common to both diseases are predominant involvement of the lymphoreticular system, eosinophilia, granuloma formation, and progressive lymphocyte depletion. Both diseases are characterized by a high risk of infection. Twoney suggested that Hodgkin's disease and AILD may be lymphocyte-depleting diseases, with the former affecting predominantly the T cell system and the latter, the B cell system. A recent report documented the termination of AILD as Hodgkin's disease in a 33-year-old man (5). The authors suggested that AILD may represent an unusual host reaction to the agent that causes Hodgkin's disease. More recently, concurrent involvement of lymph nodes by AILD and immunoblastic lymphoma was encountered in 36 patients (10). In that study, progression to immunoblastic lymphoma was observed in eight other patients in whom follow-up biopsies were performed. No significant differences in the history, clinical, or laboratory data were observed between the patients with AILD and those with lymph nodes showing AILD and immunoblastic lymphoma.

The bleak prognosis associated with AILD is recognized. Of 118 patients reported in the English literature to date (excluding those in which a diagnosis of AILD and immunoblastic lymphoma was made at initial or subsequent lymph node biopsy), only 53 were alive after a follow-up period ranging from one month to nine years. An analysis of 36 patients that were autopsied reveals multiple organ involvement (Table I) by an infiltrate composed of plasmacytoid and lymphoid cells with scattered eosinophils (2, 3, 9, 10, 20). The similarity of this infiltrate, especially with a preponderance of lymphoreticular system involvement, to graft versus host reaction has led to suggestions that AILD may represent immunoblastic transformation of B lymphocytes as a result of a drug hypersensitivity reaction (2, 3). Indeed, such infiltration may occur in graft versus host reaction. However, the degree of infiltration and tissue destruction recorded by most observers, often contributing to abnormal function of involved organs, is more characteristic of a neoplastic process than of a disease of immunologic origin (18, 21). Many patients with AILD do not give a history of allergy or drug use that would support a hypersensitivity phenomenon. Furthermore, certain gross and histopathologic features of AILD regularly are encountered in the malignant lymphomas; i.e., generalized lymphadenopathy, matting together of lymph nodes, obliteration of nodal architecture, atypical lymphoid cells, and infiltration of lymph node capsule with perinodal fatty involvement.

The present case illustrates the difficulty encountered in the treatment of patients with AILD. The lymph node indicated AILD. Accordingly, the patient was treated with corticosteroids, with temporary remission of her symptoms. The disease, however, progressed relentlessly and she expired about three months after the diagnosis.

TABLE I

*Analysis of Organ Involvement in 36 Autopsied Cases of Angioimmunoblastic Lymphadenopathy Reported in the English Literature**

Organ	No. involved by AILD
Lymph node	36
Spleen	24
Liver	18
Bone marrow	11
Kidney	5+
Lung	3+
Dura mater, esophagus skin	1 each

* excludes cases in which a diagnosis of AILD and immunoblastic lymphoma was made at initial or subsequent lymph node biopsy

+ in one large series, the number of cases in which the kidney and the lung were involved was not stated

The salient autopsy findings included massive generalized lymph node enlargement, nodular infiltration of the liver, infiltration of the vessels, bronchi and pulmonary alveolar septa, destruction of lymph node architecture with extensive perinodal invasion, and focal infiltration of the spleen, skin, and kidneys by mature and immature lymphoid and plasmacytic cells. The autopsy results were diagnosed as a diffuse malignant lymphoma.

AILD has been known to evolve into malignant lymphomas, most commonly immunoblastic sarcoma (Table II) (3–8, 10). In these cases, the diagnosis of immunoblastic sarcoma is based, not on clinical features, but on the morphology of the lymph nodes. In typical cases there is destruction of the lymph node architecture by a monomorphous infiltration of pleomorphic immunoblasts. The tumor cells are large, measuring up to 40 microns in diameter, have conspicuous nucleoli and pyrininophilic cytoplasm, and may exhibit numerous mitoses. In their description of immunoblastic sarcoma, however, Lukes and Tindle wrote: “The majority of immunoblasts of immunoblastic sarcoma, however, essentially present the cytologic features of large normal-appearing immunoblasts frequently with large or huge nucleoli and at times with multinucleation” (3). This would imply that the morphologic appearance of AILD may merge imperceptibly into obvious anaplastic immunoblastic sarcoma. If this thesis is correct, then the present case is interesting in many aspects. The tumor was composed of diffusely infiltrating, immature lymphoid and plasmacytoid cells. The pleomorphism and large cells that typify immunoblastic sarcoma were not encountered, although the diagnosis of malignant lymphoma was unequivocal. The morphology of the tumor is similar to that described by Ellman and Bloch in a patient with gamma-heavy-chain disease (23). The lymph node changes in their case were originally interpreted as Hodgkin’s disease. On review of the lesion, however, the diagnosis was reclassified as AILD that subsequently evolved into small cell lymphoplasmacytic lymphoma. Histologically, this type of malignant lymphoma appears to straddle AILD on one hand and im-

TABLE II

Evolution of AILD into Malignant Lymphomas

Authors/(Ref)	No. of cases	Age	Sex	Type of malignant lymphoma
Howarth & Bird (7)	1	7	M	Immunoblastic sarcoma
Lukes & Twindle (3)	3	—*	—	Immunoblastic sarcoma
Fisher (6)	1	28	M	Immunoblastic sarcoma & leukemia
Toth (8)	1	73	F	Immunoblastic sarcoma small cell lymphoplasmacytic lymphoma
Nathwani et al.** (10)	8	variable		Immunoblastic lymphoma
Donhuigsen (4)	3	—	—	malignant immunoblastic lymphoma
Matz et al. (9)	I	61	M	Malignant lymphoma (unspecified)
Yataganas et al. (5)	1	33	M	Hodgkin’s disease
Fayemi et al.	1	77	F	Plasmacytic lymphosarcoma

* Information not available

** excludes those cases in which a diagnosis of AILD and immunoblastic lymphoma was made in the initial lymph node biopsy (10) munoblastic sarcoma on the other. We might speculate whether or not AILD and immunoblastic sarcoma belong to a spectrum of neoplastic lymphoreticular lesions, of which the former appears morphologically more benign than the latter. This speculation is supported by karyotype abnormalities indicative of a neoplasm reported in three patients with AILD (24, 25). In addition, colchicine-sensitivity testing in two of three cases of AILD was consistent with that expected of malignant tumors of the lymphoreticular system (10). Further investigation and more extensive follow-up studies are needed to determine the exact nature of AILD.

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Renovascular Hypertension: Newer Concepts in Etiology, Diagnosis, Medical, and Surgical Management

IRWIN M. REICH, B.S.

In 1898 Tigerstedt and Bergnan demonstrated that a crude kidney extract produced hypertension in dogs; they called the active substance renin (1). Interest in this phenomenon was stimulated anew in 1934 when Goldblatt demonstrated, in a now classic experiment, that hypertension could be induced in a dog by partial constriction of the renal artery, and that the hypertension was alleviated by nephrectomy (2). This constituted the first suggestion that the kidney might be initiating a vasoconstriction response when its blood supply is decreased. Experimental renal hypertension can be further classified into the two-kidney and one-kidney models. The former is a situation where arterial pressure is elevated by narrowing one renal artery, while the second is left undisturbed. In the one-kidney model, there is renal artery constriction with contralateral nephrectomy. The two-kidney experimental model has a clear pathologic counterpart in human disease, while the one-kidney model is a more complex entity whose extension to man is less straightforward. Nevertheless, both models have contributed greatly to our comprehension of the etiologic factors in hypertension of renal origin and subsequent approaches to therapy.

The Renin-Angiotensin-Aldosterone System

Peach has recently reviewed the biochemistry of the renin-angiotensin system comprehensively, and only the salient and newest information will be briefly discussed here (3). Renin is now known to be a specific proteolytic enzyme (mol wt approx 39,500) occurring in at least five distinct forms in human plasma, which has been purified from hog plasma very recently, and still only partially purified from human plasma (4, 5). It is synthesized and secreted into the circulation by the juxtaglomerular complex of the kidney (6). While renin-like enzymes can be extracted from sundry tissues, e.g. adrenals, brain, uterus, and submaxillary glands, it has yet to be demonstrated that these substances are identical to renin, or that extrarenal sources play any physiologic role in blood pressure regulation (7–10). The stimuli for renin release arise from both changes in renal perfusion pressure and either concentration or total amount of sodium in the distal tubule, although these factors may not be entirely independent since it has been shown that a decrease in renal perfusion pressure may be followed by a reduction in sodium delivery to the distal tubule (11–14). While these factors are the probable mediators of the effects on renin release by changes in blood volume, blood pressure, sodium intake, and posture, the relative importance of these initiating phenomena remains unsettled (15). In addition to physical and chemical modulators, there are neural components in the regulation of renin release, at least in animals. These can be broken down into actions at the central, peripheral and neurohumoral levels. Thus, in dogs, renin release can be increased by electrical stimulation of the mesencephalic pressor area or the medulla near the obex and can be decreased by 50% following stimulation of the hypothalamus in conscious dogs (16–18). These responses are all obliterated by renal denervation.

Simple renal sympathectomy results in a reduction of both baseline plasma renin activity and homeostatic renin response to acute as well as chronic sodium depletion, while increased renin secretion and subsequent renal vasoconstriction result from stimulation of the renal nerves (19, 20). Infusion of epinephrine, norepinephrine or isoproterenol into the renal artery can stimulate renin secretion, and supportive studies in humans indicate that renin release in response to physiologic and pharmacologic stimuli are reduced under the influence of beta-adrenergic blocking agents (21, 22). However, the renin response to alpha-adrenergic blocking agents has been variable, and the relative importance of intrarenal vs extrarenal factors in the beta-adrenergic response remains obscure (22–25).

Finally, humoral agents other than catecholamines may play regulatory roles in renin secretion. These include: potassium ions, an infusion of which reduces plasma renin activity in both hypertensive humans and

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From the Department of Physiology and Biophysics and the Department of Surgery, Mount Sinai School of Medicine (CUNY), New York, N.Y. 10029

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normotensive controls, while potassium deprivation precedes a rise in renin release; sodium ions, whose effects have been alluded to above and which may be dissociated from the effects of potassium; antidiuretic hormone, which suppresses renin release in physiologic concentrations without affecting arterial pressure or renal blood flow; and angiotension II, which exerts a negative feedback inhibition of renin release, as described below (26–28).

The events subsequent to renin release are fairly well understood. Renin-substrate, an α_2 globulin of mol wt 57,000 (which remains to be fully purified), is produced by the liver and is hydrolized at the leu^{10}-leu^{11} bond to yield angiotension I (29, 30). This reaction occurs primarily in circulating blood but has also been noted in blood vessel walls and in the isolated nephron, and has a rather broad pH optimal range in man, 5.5–6.5 (31–33). Levels of renin substrate can be shown to be dependent on the integrity of liver function and on steroid hormone levels, e.g. estrogen administration or pregnancy, which increase baseline levels (34–37). Critically, glucocorticoid levels can increase substrate concentration as in Cushing's syndrome or after exogenous glucocorticoid administration, or they can sharply decrease substrate concentrations, as in Addison's disease (38–40).

The decapeptide angiotension I has not been clearly demonstrated to have physiologic actions of its own; rather, its importance lies in its conversion to the octapeptide angiotension II by converting enzyme, a dipeptidyl carboxypeptidase found primarily on the endothelial surface of pulmonary capillaries (41). Angiotension II is the principal effector of the renin-angiotension system, and exerts its action on three basic levels. Most importantly, it is the most potent endogenous vasopressing substance in mammals. While it is not required for blood pressure maintenance in the normal animal under normal salt intake, its presence is cricital in the face of volume depletion (42, 43). However, its cellular mechanism of action is yet to be fully appreciated.

Additionally, angiotensin II is a primary regulator of aldosterone secretion (44). This results in retention by the kidney of sodium and water which ultimately reduces renin secretion via a negative feedback loop, as previously described. Of less pathophysiologic importance are the effects of aldosterone in retaining sodium in sweat glands, and in enhancing sodium absorption in the gut. Aldosterone also promotes the secretion of potassium into the urine by the kidney distal tubule cells, via a mechanism believed to be independent of sodium retention. Precisely how aldosterone exerts its action at the cellular level remains to be defined, but recent work in the toad urinary bladder suggests that aldosterone unmasks the transcription of mRNA which codes for plasma membrane proteins, which in turn, may be acting either to increase luminal permeability to sodium, or to increase serosal Na-K ATPase activity (45). The net effect is an expansion of plasma volume which may be hypertensive in itself, as in the hypertension of primary aldosteronism, or it may exacerbate the hypertension caused by a generalized increase in the activity of the renin-angiotensin-aldosterone axis.

The central nervous system is the third site of action of angiotensin II, where the area postrema (a medullary region lacking a blood-brain barrier) is believed to be the principal target of the hormone, the primary effect being a decrease in vagal tone to the heart (46, 47).

The classical concept of the renin-angiotensin system has been extended to include angiotensin III, a des-Asp^1 heptapeptide, derived from angiotensin II by angiotensinase in circulating blood and known to exert a strong in vitro ionotropic effect on papillary muscle as well as being a potent stimulator of aldosterone synthesis in adrenal cell suspensions (47–49). However, the in vivo effects of this peptide remain to be elucidated.

Etiology of Renovascular Hypertension

The origin of elevated blood pressure as a consequence of the narrowing of the renal artery can be understood in view of the physiologic mechanisms just described. Renal artery or afferent arteriole constriction result directly in decreased pressure as well as decreased delivery of sodium to the distal tubule. It has been demonstrated that there is a pressure drop across the experimentally constricted renal artery, provided the diameter is reduced more than 60% (50). Although contradicted by Bounous and Shumaker, Levy and associates showed that Goldblatt clamping produced an average decrease in renal blood flow of 41% with a range of 30 to 63% (51, 52). These data are confirmed by May et al who found that, in man, an 82%–97% reduction in renal artery cross-sectional area is associated with a significant decrease in pressure in the distal tubule (53).

In response to renal artery constriction, renin is secreted and the homeostatic mechanisms of the renin-angiotensin system are brought into play (54). Upon restoration of normotension, renin secretion is lowered to baseline levels via the negative feedback loops, as outlined. Thus, elevation of both renin and angiotensin II have been demonstrated in the two-kidney Goldblatt experimental model and blood pressure can be lowered by the administration of saralasin (1-sarcosine-8-alanine angiotensin II), an angiotensin II blocking agent (55, 56). This concept has recently been extended to man (Fig. 1). However, in the one-kidney Goldblatt model there is only a transient initial elevation of renin followed by a sodium volume dependent phase characterized by normal renin and angiotensin II levels when the hypertension produced is refractory to angiotensin II blockage (57, 58). Similarily, administration of an antirenin antibody to rabbits with experimental renovascular hypertension will alleviate only the early portion of the hypertensive course (59). Angiotensin II is also responsible for the initial

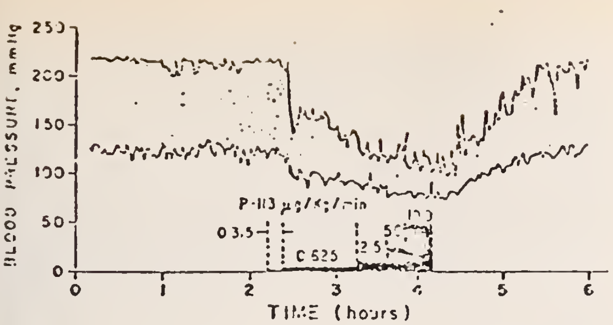

FIG. 1. Effects of Saralasin infusion on the blood pressure of a patient with renal artery sterosis and high plasma renin activity. Infusion proceeded from t=2.25 hours to t=4.25 hours. From Streeten et al, New Eng J Med 292:657, 1957. Reproduced by permission.

hypertensive state in the one-kidney model; this has been demonstrated by the complete reversal of the hypertension by infusion of an inhibitor of converting enzyme (60). Recently, it has been demonstrated that the two-phase mechanisms involved in the one-kidney model may also be active in the two-kidney model, the difference being in a prolongation of the time required to reach the second phase (61). It is believed that the initially normal kidney under continued exposure to hypertensive insult, possibly in combination with elevated renin levels, may eventually undergo secondary vascular damage leading to impaired sodium excretion and, ultimately, volume expansion with suppression of renin secretion from the clipped kidney (62). Laragh and coworkers hypothesized that a similar mechanism may be applicable in renal hypertension and even certain forms of essential hypertension in man. In view of this, hypertensive patients with normal renin levels might actually have had previously elevated renin levels and subsequent kidney damage sufficient to sustain the hypertensive state even if renin levels fell (61). Supporting this concept is the finding that patients with essential hypertension and low renin levels are older than essential hypertensive patients with normal renin levels (63).

Diagnosis of Renovascular Hypertension in Man

Renovascular hypertensive disease is the most common form of correctable hypertension. The prevalence has been estimated at ten percent and possibly as high as 36 percent of all hypertensives (64). However, a recent study showed that of 26,589 patients who had diastolic pressures ≥95 mm Hg, renal artery stenosis repair was performed in only 0.18%, suggesting that this condition is much less common than generally believed. The authors hyothesize that their relatively broad definition of hypertension may account for the discrepancy between their figure and that of previous investigators (65). While there are many possible causes (Table I), atherosclerotic degeneration of the renal artery is the causative entity in two-thirds of patients, usually occurring after age 40. This lesion is not necessarily associated with clinical hypertension (66).

The second most common cause is fibromuscular dysplasia, which usually appears before age 40 and which occurs more frequently in females than in males at a ratio of 4:1(67). The etiology of this lesion remains a subject for investigation. Dornfeld and Kaufman have recently advanced the interesting proposal that in some cases there may be immunologic mechanisms involved, possibly similar to the immunologic processes responsible for some diseases of the renal parenchyma (68). They present four cases of fibromuscular dysplasia in which hypertension-related renal artery lesions followed a history of repeated upper respiratory tract infections. In three of the cases there was pathologic evidence suggestive of vasculitis, and in the fourth patient they obtained marked clinical improvement of associated myalgias and joint stiffness after prednisone therapy. Vessels taken from one patient during surgery showed a granular, nodular deposition of IgM, complement, and fibrinogen at the luminal edge of the intima. Dysplasias are usually found in the middle or distal two-thirds of the renal artery although segmental branches may be involved, and the lesion may be bilateral. In 64 percent, there is medial fibroplasia with mural aneurysm; in 20 percent there is perimedial fibroplasia; medial hyperplasia occurs in 10 percent; and the remaining lesions show intimal fibroplasias, medial dissection, or adventitial lesions (69). Other lesions such as renal artery aneurysms, arteriovenous fistulae, and renin-secreting tumors are rare. In addition, there are renal parenchymal diseases which may correlate with a hypertensive course, that are not

TABLE I

Causes of Potentially Curable Renal Hypertension

- Obstructive uropathy
- Renal artery occlusive disease
  - Arteriosclerosis
  - Fibromuscular hyperplasia
  - Aneurysm
  - Aortitis with renal artery stenosis
  - External compression
    - Tendon, foreign body or
    - Tumor—renal or retroperitoneal
- Embolism: clot, foreign body
- Coarctation of aorta
- Arteriovenous renal fistula
- Renal vein occlusive disease
- Pyelonephritis
- Tuberculosis
- Hydronephrosis
- Tumor
- Nephroptosis
- Radiation nephritis
- Marfan's syndrome
- Post-traumatic perinephric fibrosis

Reprinted with permission from Rob, C.G. and McDonald D.F.: Renal Hypertension, Adv in Surg 1:111, 1965. Copyright © 1965 by Year Book Medical Publishers, Inc., Chicago. Used by permission.

amenable to surgery. These include glomerulonephritis, polycystic disease, collagen vascular disease, diabetes mellitus, gout, and nephrocalcinosis (70).

Some clinical clues are available to help identify the hypertensive patient who will ultimately be found to have renovascular pathology. The history may reveal a relatively sudden onset of hypertension, often after age 50; the onset may have followed an episode of flank pain. The family history will be negative more often than not. Malignant hypertension may be a feature, usually after age 55. In contrast with those who have essential hypertension, these patients are more likely to be caucasian and thin. However, some patients with demonstrated renovascular hypertension may have none of these characteristics (71). On physical examination, the most distinguishing finding is the presence of an abdominal or flank bruit, found in 50% to 80% of patients with renovascular disease, while present in less than 5% of essential hypertensives (72, 73). This is a more constant sign with fibromuscular hyperplasia than with atherosclerosis. Also, in fibromuscular disease the bruit is more likely to be soft and continuous, while in atherosclerotic lesions, it is apt to be a high-pitched, systolic bruit.

The initial workup is the same as for any hypertensive patient and includes urinalysis with culture, chest x-ray, and EKG. An SMA-18 is done with attention paid to the serum potassium, BUN and creatinine concentrations, in an effort to exclude hyperaldosteronism (either primary or secondary) or intrinsic renal disease as the underlying pathology. More specific workup may include urinary catecholamine determinations to rule out pheochromocytoma.

If these tests are inconclusive, the patient may be evaluated for renovascular disease. Peripheral venous plasma renin activity (PRA) may be measured; values greater than 400 ng AII/100 ml are strongly suggestive of renal artery stenosis, in the presence of a normal dietary sodium intake and in the absence of malignant hypertension or diuretic therapy (74). Within the past few years, a screening test has become available using the angiotensin II blocking agent, saralasin, which probably will replace rapid sequence intravenous pyelography as the next step in this specific workup (Table II). Streeten found that he could differentiate between patients with high plasma renin activity who respond to IV infusion of saralasin, and those with normal or low PRA whose hypertension is refractory to saralasin (Fig. 1) (75). Salt-restricted hypertensive patients with either elevated peripheral venous PRA or abnormal renal vein renin ratios responded to saralasin with a mean fall in diastolic pressure of 27 mm Hg. This approach is also advocated by Peart and Laragh (76, 77). The nonresponding patients may be subsequently evaluated for other possible etiologies of their hypertension.

TABLE II

Patient Evaluation

- Screening—Angiotensin antagonism
- Evaluation
  - Excretory urogram
  - Renal arteriogram
  - Bilateral renal vein renin assay
- Supplementary, confirmatory tests
  - Isotopic renography scans and function tests
  - Differential renal function tests

Preoperative evaluation of patients suspected of having renovascular hypertension.

From Rob, C. and Frank, I.N.: Renal Artery Occlusive Disease with Hypertension, In *Rhoads Textbook of Surgery*, J.D. Hardy (ed.), pp. 1803–1807. J.B. Lippincott, Philadelphia, 1977. Reprinted with permission.

TABLE III

Parameters Which Suggest Unilateral Renal Ischemia on Intravenous Pyelography

1. One kidney is 1.0–1.5 cm. shorter than the other.
2. When opaque medium is very rapidly injected a 15 second film shows delayed nephrogram.
3. When opaque medium is injected rapidly delayed excretion of opaque is seen on the ischemic side in 2, 3, 4 minute films.
4. Thickness of substance of the kidney, measured from middle calyx to edge of kidney shadow, is unilaterally reduced. Depressed focal scars alter renal silhouette and distort calyces, chronic pyelonephritis or infarcts.
5. Calyces and infundibuli of one kidney are thin and very discrete, so-called spider or spastic calyces.
6. A crescent of calcific material in the region of the renal artery may indent the renal pelvis, a renal artery aneurysm.
7. There is irregular notching of the upper ureter indicating collateral arterial circulation from ureteral vessels.
8. On 15–30 minute films there is hyperconcentration of contrast medium on the ischemic side.
9. On a repeat intravenous pyelogram when the patient is hydrated the normal kidney fails to visualize whereas the ischemic kidney visualizes normally.
10. There is unilateral nonvisualization.

From Rob, C.G. and McDonald, D.F.: Renal Hypertension, Adv in Surg 1:111, 1965. Copyright © 1965 by Year Book Medical Publishers, Inc., Chicago. Used by permission.

After PRA and saralasin-response tests have been performed, an excretory urogram may be obtained. The criteria supporting the diagnosis of unilateral renal ischemia are listed in Table III. Most suggestive is when there is a difference of 1.0 cm or greater in the length of the kidneys or when there is an initial delay in the appearance time or decreased concentration of the contrast medium. The latter finding may be positive in up to 94% of patients with main renal artery stenosis. The remaining criteria, however, are less frequently positive. A finding of a difference in concentration on late films is the most frequent falsely positive reading (64). When the major criteria are fulfilled there is an 80 percent correlation with subsequent angiographic confirmation of renal artery stenosis. The overall false-positive and false-negative readings of the films are each approximately 10%. The most important limitations of the technique are in the detection of bilateral renal artery disease and segmental arterial disease (71).

The excretory urogram is followed by renal arteriography, which can definitively localize the arterial lesion in those patients who are being considered for eventual surgical correction. The technique consists of percutaneous retrograde transfemoral arteriography, and the performance of flush aortography in conjunction with selective renal arterial injections of contrast media which may demonstrate segmental vascular lesions (78). The films also reveal the extent of poststenotic dilatation and collateral circulation, but successful surgical response bears no correlation with these findings. While arteriography is critical in defining the nature (atherosclerotic, fibromuscular dysplasia, or aneurysm) and potential for surgical intervention, it is done bearing in mind that there may be renal artery occlusion which is not the causative factor of the patient's hypertension, and the films should be examined for evidence of primary renal malignant tumors or benign, renin-secreting lesions (71, 79). Complications of the procedure may include hemorrhage, thrombosis of femoral or iliac arteries, or renal injury, but in a recent series of 2,089 transfemoral catheterizations the mortality and morbidity rates were only 0.11 percent and 1.2 percent, respectively (80).

The demonstration of a renal vascular lesion does not invariably implicate it causally in the etiology of the hypertension, so that renal function tests must now be performed. A test that has been closely correlated with a causally significant radiologic abnormality is the renal venous renin ratio. A renal vein renin concentration of the involved kidney more than 1.5 times the value of the contralateral side, constitutes good evidence of significant renin secretion, and correlates well with anatomic pathology. If the test results are equivocal in spite of strong suspicion, the sensitivity may be enhanced by prior renin stimulation via salt depletion, diuretics and the upright position. Hypertensive patients who have normal renal arteries rarely have a renal vein renin ratio greater than two (74). The use of this test in conjunction with peripheral renin concentrations is advocated by Vaughan and Laragh for predicting surgically curable renovascular hypertension (see Indications for Surgery).

There is some disagreement in the literature on how to proceed at this stage of the workup. Some authors advocate radioisotope renography for evaluation of kidney function and renal blood flow as the next step, arguing that more information concerning the vascular integrity of the kidneys may be gleaned. This may be helpful in the selection of patients for surgery (79). Others object, citing a 20 percent false-positive rate among patients with essential hypertension, and a false-negative rate of 14%. In addition, although the technique can show a functional disparity between two kidneys, it cannot distinguish renal artery stenosis from unilateral renal parenchymal disease (70, 71, 81). However, improved technology may increase the usefulness of this test in the future.

Controversy also exists concerning the role of split-function tests in patient evaluation. This involves bilateral ureteral catheterization and measurement of U_v (ml/min), U_{Na} (mEq/L), $U_{creatinine}$ (mg/%) and U_{PAH} (mg/100 ml). First popularized by Howard and Stamey, the criteria call for demonstrating specific, significant differences in these parameters between the involved and normal kidneys (82, 83). Most authors today, however, believe the tests to be excessively complicated by technical difficulties in up to 20 percent, and occasionally responsible for infection or renal shutdown (84, 85). In addition, the test results have no significant correlation with arterial pressure response to surgical correction, bearing a high incidence of false positives and false negatives. Rob and Frank, however, maintain that the tests should be performed in selected cases where there is a high index of suspicion and the renin assays do not confirm the clinical and radiologic findings (79).

Medical Management

The medical treatment of renovascular hypertension may be a symptomatic approach similar to that used in essential hypertension, or it may be more specifically directed at inhibiting any of the steps in the renin-angiotensin-aldosterone axis. Symptomatic relief may be obtained by the use of diuretic therapy or drugs such as hydralazine and guanethidine. Specific therapy is available in the form of spironolactone which interferes with the binding of aldosterone to its receptors in the renal distal tubule cells. However, specific treatment ideally should act in the system before the level of aldosterone, i.e., inhibiting the release or actions of renin, angiotensin I, or angiotensin II, since angiotensin II exerts a marked hypertensive effect via vasoconstriction even without the additional insult effected by aldosterone's contribution to the expansion of plasma volume. In practice, the drug most widely used for specific therapy is the β-adrenergic blocking agent, propranolol, which is capable of inhibiting renin release. Saralasin is being used experimentally, as is a new compound which inhibits the angiotensin-converting enzyme, designated SQ20,881 (<Glu-Trp-Pro-Arg-Pro-Glu-Ile-Pro-Pro) (86). The latter has recently been found to be of value in the diagnostic workup of renal artery stenosis (87). Particularly promising is the very recent development of an orally active inhibitor of angiotensin-converting enzyme, designated SQ14,225, which has been demonstrated to have a significant antihypertensive effect in Goldblatt two-kidney renal hypertensive rats (88). Although shown to be effective (89), this drug awaits further clinical trials. Pharmacologic efforts are also being made to develop drugs which will act as competitive inhibitors of renin action (90).

An early report of a group of patients whose renovascular hypertension was managed medically came from the Cleveland Clinic in 1963 (91). The drugs used included hydralazine, guanethidine, and hydrochlorothiazide, alone and in combinations. Of thirty-two patients followed for periods ranging from one to five years, three became spontaneously normotensive, 11 obtained normal diastolic pressures with therapy, and 18 remained hypertensive including five who received no therapy. These results may be viewed in a more encouraging light since all the conservatively managed patients were considered poor surgical candidates because of diffuse atherosclerosis, azotemia from severe nephrosclerosis, unsustained diastolic hypertension, or because no disparity in function between the two kidneys could be demonstrated. Results from ten patients who were followed carefully for a mean period of 20 months showed an average decrease in blood pressure from 200/112 mm Hg to 167/87 mm Hg. Unfortunately, the follow-up period for this group might have been longer, and the study used patients rejected for surgery rather than random selection. Also, it was not made clear as to why all of the patients who failed to respond were ascribed to inadequately supervised treatment. Lastly, the patients were not stratified as to the nature of their lesions, whether atheromatous or fibromuscular.

Sheps et al presented data on the medical management of 54 patients, 32 with atherosclerotic lesions and 22 with fibromuscular dysplasia (92). The patients had been excluded from surgery because they preferred a medical program, the anatomic location of their lesion technically demanded nephrectomy, the stenosis was not severe, the hypertension was not severe, or the symptoms suggested significant compromise of either coronary or cerebral blood flow. For the atherosclerotic group, the mean age was 53.6, and the mean pretreatment blood pressure was 200/119 mm Hg; 22 patients in this group had EKG changes indicative of left ventricular hypertrophy. For the fibromuscular group, the average age was 41.3, and mean blood pressure before treatment was 188/116 mm Hg; only six patients in this group had EKG changes. All patients were evaluated for renal function and generally the functional abnormalities corresponded with the arteriographic lesions. The therapy in almost all cases consisted of a thiazide eiher alone or in combination with reserpine, hydralazine, or guanethidine; the average follow-up time was 20.3 months. Five deaths occurred during the study, all among the atherosclerotic group. Of the remaining 49 patients, 65 percent were rendered normotensive, with a mean blood pressure of 154/93 mm Hg. However, it was not clarified why, after having stratified the pretreatment data into atherosclerotic and fibromuscular groups, the posttherapy data were not similarly reported. Also, the authors acknowledge that because of their patient selection, their series did not constitute a control group for surgically treated patients. Nevertheless, they advanced recommendations for a conservative course of management when: (1) the situation technically demands nephrectomy; (2) there is no significant hypertension in spite of demonstrable renovascular lesions; (3) there is disparity between the arteriographic and renal function data; and (4) there is associated severe symptomatic cardiovascular disease or old age.

The results of a study by Shapiro and coworkers of 115 patients, 43 of whom underwent surgery, are less encouraging for advocates of medical treatment (93). However, again the nonoperative group was not selected randomly, and the authors state that "the manner of surgical selection was such that the unoperated patients were probably those with the poorer prognosis." Despite copious reporting of the patients' characteristics, certain basic parameters were not disclosed, including the details of medical therapy and the average period of follow-up (range: one to six years). At the last follow-up, forty percent of the medically treated group were dead.

More recently, publications have appeared with the results of more specific treatment. Buhler and coworkers found that in 13 hypertensive patients with high PRA values, propranolol was uniformly effective, producing a mean decrease in diastolic pressure of 30 mm Hg, and that in 22 patients with normal PRA values, propranolol was generally effective, reducing the mean diastolic pressure by 20 mm Hg, while in 12 patients with low renin essential hypertension, the drug was uniformly ineffective (94). The antihypertensive action of propranolol was found to be closely related both to the control level of PRA and to the capacity of the drug to inhibit renin release. Ten of the patients were diagnosed as having renovascular disease, five in the high renin group and five in the normal renin group; they were not further classified as having either atherosclerotic or fibromuscular lesions. The fall in diastolic pressure was consistent among these ten patients, the mean drop being 27.0 ± 8.6 mm Hg. The authors concluded that the major antihypertensive effects of propranolol were due to its renin-inhibiting properties rather than to its depression of cardiac output, and that patients with high renin hypertension, whether renovascular, malignant or essential, respond strikingly to this therapy. However, the study cannot be readily used as a comparison for renovascular hypertensives treated surgically because of the lack of randomized selection of patients.

In a follow-up study by the same investigators, eleven patients with either renal artery disease (n = 8) or unilateral parenchymal disease (n = 3), as documented by pyelogram, renal arteriography and renal vein renin studies, were evaluated for their response to propranolol therapy (95). The drug was administered in doses of two to six mg/kg (mean 3.2) for an average duration of 57 days. Pretreatment high renin values were obtained from three of the patients with renovascular disease and from two with unilateral renal disease; the rest had normal renin values. All but one of the high-renin patients responded to propranolol treatment, whereas the response in the patients with normal renin values was more variable. This group of patients was then subjected to either renovascular surgery (n = 4) or uninephrectomy (n = 7). There was a striking correlation between the blood pressure responses to propranolol and to surgery. The best responses to both therapeutic modes were obtained in the patients who had high renin activity before treatment, in whom the abnormal renin contribution originated from the involved kidney, and in whom contralateral renin secretion was suppressed (96, 97). Of even greater interest was the fact that there were six patients with normal peripheral plasma renin whose responses to propranolol correctly predicted the success of surgical intervention. Thus, the authors suggest that propranolol-responsiveness may prove to be a useful screening test for possible surgical intervention in patients suspected of having renovascular hypertension.

Within the past two years, several groups have presented data on the management of essential hypertension with propranolol, which confuses the concept of the drug acting exclusively via a renin-suppressing effect. Hollifield et al studied the effects of high doses (320 to 960 mg daily) of propranolol in seven high renin patients, and found that there was no significant change in PRA values even though blood pressures did drop significantly (98). Furthermore, high dose propranolol was effective in lowering blood pressure in low renin patients, and there was no statistically significant difference in the magnitude of propranolol's antihypertensive effects between the high renin and the low renin groups. The authors infer that the drug is acting through a dual mechanism, and speculate that in addition to renin-inhibition there is a central nervous system effect. In an attempt to further define the mechanism of propranolol's action, Mookherjee and coworkers found that propranolol in doses of 2 mg/kg/day significantly lowered both mean blood pressures and PRA in six of nine low renin essential hypertensives, and that heart rate and cardiac output also declined, as expected (99). High and normal renin patients were also included in the study. However, when PRA and blood pressure changes were evaluated in tandem, it was found that there was no association between lowering of PRA and lowering of mean arterial pressure. In addition, stroke volume increased and corrected ejection time and total peripheral resistance remained unchanged during treatment. The results were interpreted as showing that propranolol does not exert an antihypertensive effect related to its hyporeninemic effect, nor could the fall in cardiac output account for the reduction in blood pressure. The overall question of precisely how propranolol exerts its action clearly remains open to further investigation.

Surgical Management

The operative approach to renovascular hypertension is aimed at removing the offending lesion, hence curing the symptom complex. Although this paper is not primarily concerned with the surgical procedures available, a brief synopsis is warranted. The following approaches may be used in renovascular hypertension: revascularization either by reconstruction or bypass, nephrectomy, or partial nephrectomy. Most commonly, a segment of saphenous vein is used to construct a bypass graft anastomosed to the side of the abdominal aorta and to the renal artery distal to the anastomosis (100). A Dacron bypass graft is also feasible. If the lesion is a well-localized atherosclerotic plaque, thromboendarterectomy is an excellent alternative. Segmental resection with reanastomosis is not usually done, but is possible if the proximal and distal ends of the vessel are suitable. Most authors believe that anastomosing the splenic artery to the distal renal artery should be reserved for situations where other options are technically impossible, but others claim the procedure generally yields good results (71, 79, 101). Nephrectomy is reserved for cases where arterial repair may be dangerous and where the disease is likely to remain unilateral, but the procedure can yield excellent results. Other possibilities of use in special situations are repair by vein patch angioplasty, placing an arterial autograft, constructing a prosthetic arterial graft from the aorta to the distal renal artery, and dilatation of the stenotic segments in some patients with fibromuscular hyperplasia.

The relative frequency of various procedures in a typical series is presented in Table IV, taken from Foster et al (101). In 122 patients, vein bypass grafts were used in almost half, and nephrectomy was employed in approximately 20%. Both procedures were relatively more common in patients with fibromuscular dysplasia, reflecting the greater use of thromboendarterectomy in athero-

TABLE IV

Primary Operative–Procedures

Procedure	Fibromuscular Dysplasia	Atherosclerotic	Total
Vein Bypass Grafts			
Single Aorto-Renal	22	25	47
Bilateral Aorto-Renal	3	5	8
Dacron Bypass Grafts			
Single Aorto-Renal	1	10	11
Bilateral Aorto-Renal	1	7	8
Thromboendarterectomy (TEA)			
Single	3	13	16
Bilateral		3	3
Nephrectomy	11	15	26
Other			
Autogenous Arterial Bypass	3		3
	44	78	122

Surgical procedures in 122 patients with renovascular hypertension. From Foster J.H. et al: Ten Years experience with the Surgical Management of Renovascular Hypertension, Ann Surg 177:755, 1973. Reproduced by permission.

sclerotic stenosis. The study is also notable for having listed the relative frequencies of the nonfatal postoperative complications experienced (Table V). By far the most common was thrombosis of the bypass or thromboendarterectomy, followed by congestive heart failure and acute tubular necrosis. Causes of surgical mortality in renovascular patients may be appreciated from the series of Franklin and his colleagues, where the data is further stratified according to the particular procedure used (102). Uremia was most common overall, hemorrhage was most common when unilateral reconstruction was attempted, and myocardial infarction was most common when the procedure was unilateral nephrectomy, total or partial.

TABLE V

Complication	# Patients
1. Thrombosis of Bypass or TEA*	24
2. Congestive Heart Failure	4
3. Acute Tubular Necrosis	4
4. Intestinal Obstruction	2
5. Aortic Suture Line Disruption	1
6. Basilar Artery Thrombosis	1
7. Hemolytic Crisis	1
8. Bracheal Plexus Stretch Injury	1
9. Renal Arterio-Venous Fistula	1
10. Abdominal Angina	1

* TEA = Thromboendarterectomy

Complications of surgical treatment of renovascular hypertension in 122 patients undergoing 148 procedures.

From Foster J.H. et al: Ten Years Experience with the Surgical Management of Renovascular Hypertension, Ann Surg **177**:755, 1973. Reproduced by permission.

Recently, the approach of arterial reconstruction has been extended in patients with fibromuscular hyperplasia or aneurysms where the secondary renal artery branches are involved. Belzer and his associates at the University of California at San Francisco reported two patients, each of whom had stenosis of renal artery branches demonstrable on arteriography (103). The basic technique calls for extracorporeal hypothermic continuous pulsatile perfusion, with the ureter mobilized to permit an ex-vivo procedure. The secondary renal artery branches are then either reconstructed or replaced with saphenous vein or hypogastric artery grafts; the kidney is finally either replaced or autotransplanted to the side of the iliac vessels. Patients with bilateral fibromuscular hyperplasia extending beyond the segmental branches are candidates for this approach. Another even newer approach is that of visceral bypass wherein a saphenous vein graft is used to bypass the hepatic and/or splenic arteries to the corresponding renal artery (104). This procedure is still under investigation.

Studies reporting the results of surgical management of renovascular hypertension have been collected and summarized (Table VI). Aggregating patients from different research groups may be hazardous because of possible differences in criteria for patient selection and specific therapeutic techniques. Bearing this in mind, however, the summary indicates that of 2206 patients, 48% were cured and 77% at least were improved, with an

TABLE VI

Summary of Experience with Surgical Approach to Renovascular Hypertension

Report	Year	No. of Patients	Cured (%)	Cured and Improved (%)	Operative mortality (%)
Michigan (119)	1962	43	40	82	4.0
Cleveland Clinic (91)	1963	76	62	78	10.0
UCLA (120)	1964	67	37	82	4.0
Baylor (104)	1966	432	41	81	7.0
Vanderbilt (121)	1966	35	46	77	6.0
Mayo Clinic (122)	1967	100	55	84	0.0
UCSF (123)	1967	122	37	65	8.0
Virginia (124)	1968	53	28	75	3.6
UCSF* (125)	1969	41	22	56	15.0
UCSF* (125)	1969	42	26	74	2.4
Columbia (126)	1970	40	53	76	2.5
Mayo Clinic** (127)	1970	46	46	66	6.0
Vanderbilt (128)	1971	81	70	90	3.6
Mayo Clinic (106)	1973	100	51	78	1.0
Mayo Clinic (129)	1974	75	—	85	2.7
Vanderbilt (101)	1975	122	59	90	5.4
Cooperative Study (107)	1975	502	51	66	5.9
Michigan*** (109)	1975	113	55	95	0.0
Columbia (110)	1976	116	66	85	0.0
Total		2206			
Average			48	77	5.0

* Atherosclerotic lesions only.

** All patients had aortic occlusive disease or aneurysm in addition to renal entry stenosis and operative treatment of both.

*** Fibromuscular dysplasia only.

operative mortality of 5.0%, all on a weighted average.

It would be useful to select some of these studies for further detailed discussion, to illustrate the problems as well as the progress in both the reporting as well as the actual results of the surgical approach. In the Cleveland Clinic series, patients were selected for operative treatment as the standard therapy provided they were not excluded for the reasons mentioned under Medical Management (91). The acute operative mortality rate was ten percent, and another 12 patients died during follow-up, which ranged from one to six years. However, of 99 patients, 44 became normotensive postoperatively, and 15 patients obtained significant reduction from preoperative levels, while 17 patients experienced no clinical improvement. Overall, while the study was notable as the first organized attempt to compare medical therapy with surgery, the patients were not randomly alloted and the results of the two groups could not be considered significantly different; when the difficulties in experimental design were taken into account, it could not justify displacing potentially curative surgery as the usual mode of treatment. The data did indicate, however, that there was a reasonable alternative to surgery for selected patients with either unsustained hypertension or clinical features which rendered them poor risks for surgery in general.

Similar conclusions could be drawn from the work of Shapiro and his associates (93). Again, bearing in mind that patients were carefully selected for each therapeutic modality, one-third of the operative group experienced either cure or marked improvement. At the end of the follow-up period, another thirty-five percent of the postoperative patients were dead, as compared to forty percent of the medically managed group.

In 1966, Morris and his coworkers at the Baylor University College of Medicine described the results of 432 patients with renovascular hypertension (105). Patients were selected on the basis of demonstrated renal artery stenosis by IVP, arteriography, renal scan, renogram, and in some patients, renal artery function studies with ureteral catheterization. The mean age was 50, atherosclerosis and fibromuscular hyperplasia accounted for 73.1 and 11.6 percent of the lesions respectively, the remaining 11.1 percent being an aggregate of bands, kinks, traumatic or inflammatory lesions, and congenital or developmental defects; however, the results were not broken down according to the nature of the lesion. The mean preoperative blood pressure was 206/115 mm Hg. In most patients surgery consisted of either bypass or endarterectomy. There was an acute mortality rate of seven percent and an annual death rate of three to five percent for the five-year-postoperative period. Unfortunately, no information was supplied concerning the patients' related cardiovascular problems, e.g. history of myocardial infarction or CVA, which might have influenced the significance of these figures. One year postoperatively, 81% of the patients were significantly improved, including forty one percent who had become normotensive. In 245 of the 432 patients, follow-up arteriography was used, which indicated 8.6 percent (36 patients) with at least renal artery stenosis. Seventeen of these were treated medically and nineteen had a second operation. Four years after surgery, 68% of patients remained markedly improved, although this declined to 44% during the fifth year. After five years, 68% of the patients were still alive. Because of its size, the series formed the basis for operative treatment for approximately six years after its publication, despite its deficiencies in experimental design and in reporting of important parameters. The participating patients could not be easily used as a basis for comparison with a medically treated group, primarily because the same investigators did not carry out an alternative course of drug therapy, and because of the lack of randomized selection of patients.

The next major series came from the Mayo Clinic in 1973, representing 214 cases followed prospectively for seven to 14 years; this is the longest follow-up period yet on record (106). Because long-term observation was desired, patients were highly selected for relative youth, which skewed the incidence of fibromuscular stenosis to 133 of the cases while only 81 patients had atheromatous lesions; correspondingly, there were more female patients (n = 125) than male (n = 89). The data was reported separately for the two etiologic groups throughout. The mean blood pressure of the atheromatous group preoperatively was 212/124 mm Hg, that of the fibromuscular group 194/222 mm Hg. All patients were given an initial trial of medical therapy which included control of dietary sodium, up to 100 mg hydrochlorothiazide daily, and possibly, the addition of spironolactone, methyldopa or guanethidine. Those who failed to respond adequately after three months (n = 100) were chosen for surgery, while the remainder (n = 114) were continued on antihypertensives. The average blood pressure of the medical group was somewhat less than the surgical group; nevertheless, the results supported surgical intervention as the preferred mode of treatment. At a mean follow-up interval of 8.8 years, 26 of 37 surgical patients with atheromatous lesions were still alive, 24 of them being maintained with diastolic blood pressure <90 mm Hg without medication (n = 12) or with mild antihypertensives (n = 12). Of 63 surgical patients with fibromuscular lesions, a remarkable 58 were still alive after the same period, 39 of whom maintained low diastolic blood pressures without medication and another 15 requiring only mild antihypertensives. These data were compared with the results of the medically-treated group: at a mean interval of 9.0 years, 27 of 44 atheromatous patients had died and another 7 had been transferred for surgery (although their results were not included in the surgical group), while 12 of 70 patients with fibromuscular disease had died and another 9 had required surgery. The 39 deaths in the medical group were ascribed to myocardial infarction (n = 21), CVA (n = 8), renal failure (n = 8) and unrelated causes (n = 2). The overall death rate at the last follow-up study was sixteen percent among surgical patients and forty percent among medical patients. Despite the lack of detailed reporting of associated medical problems at the time of selection, as well as the lack of randomization, this study provided the strongest support yet for surgical treatment, especially in young patients without symptomatic coronary artery disease.

Similarly, encouraging postoperative results were obtained by Foster and his associates, although they did not concurrently follow a group on medical therapy (101). A total of 122 patients were followed, 78 with atherosclerotic lesions and 44 with fibromuscular dysplasia. The average preoperative diastolic blood pressure in both the patients with atherosclerotic stenosis and those with fibromuscular disease was reported as 105 to 140 mm Hg. Again, the data were especially optimistic for the fibromuscular patients, 72% of whom were cured, and an additional 24% of whom obtained a diastolic blood pressure between 90–100 mm Hg after a reduction of at least 20 mm Hg. The patients who had atheromatous lesions experienced a 53% cure rate while 36% were similarly improved. Twenty-six patients required a second operation. Overall, there were eight operative deaths and only four failures. On follow-up (six months to 11 years; mean period not reported) nine patients, all from the atherosclerotic group, including one of the initial failures, died within five years. The three other failures remained so, but the remaining 102 patients were either cured or improved when last seen. Development of a significant lesion distal to a previous bypass was not encountered. The authors concluded that about 90% of all renovascular hypertensives may obtain a beneficial result from surgery.

The largest series to date of surgically-treated renovascular hypertensive patients was published in 1975 as the result of a cooperative study of fifteen participating university hospitals (102, 107, 109). A total of 880 renovascular patients were collected out of 2,442 hypertensives; 502 were operated on for a total of 577 surgical procedures, and 384 were followed for at least one postoperative year. Diagnosis was made on the basis of the usual hypertension workup and included rapid sequence intravenous urogram, radioisotope renogram, individual kidney function tests, and renal arteriography. Of the 502 patients there were 300 cases of atherosclerotic lesions, 179 cases of fibromuscular hyperplasia, and 23 cases of miscellaneous renal artery lesions. The age distribution of each of the two major etiologic groups was plotted, including all 838 renovascular patients, and further stratified according to sex. The mean ages were similar for males and females in both the atherosclerotic patients (m = 52.1; f = 51.2) and the fibromuscular hyperplasia patients (m = 38.6; f = 40.2); however, there were significantly more cases of fibromuscular disease among females than males in the pediatric age range. Unilateral disease was formally defined as: (1) renovascular disease of any severity on one side only, with no stenotic lesion demonstrable on the contralateral side, or (2) renovascular disease with greater than 25% stenosis on one side and no lesion or stenosis of less than 25% on the opposite side. Ipsilateral segmental lesions did not alter this definition, and bilaterality was defined as any renovascular disease not fitting the criteria for unilateral disease. Ninety-four of the operative atherosclerotic group (31%) and 43 of the fibromuscular hyperplasia group (24%) had bilateral lesions.

The primary surgical procedure was unilateral or bilateral reconstruction in 315, nephrectomy in 168, partial nephrectomy in ten, and reconstruction with contralateral nephrectomy in nine patients. Two procedures were required for 67 patients and three procedures were required for four patients. However, the decision regarding the indications for surgery were left to the discretion of each participating group, which the authors concede resulted in some institutions relying primarily on the results of the renal arteriogram, some upon the individual renal function tests, and some upon the IVP. This was probably the major weakness in the experimental design of the study, and it was, therefore, impossible to evaluate the incidence of false-negative results for each of these tests. It also rendered the data of all the parameters collectively subject to skewing in unknown fashions, the significance of which is impossible to estimate. Additionally, there were important omissions in data collection with regard to clinical characteristics as a result of the elimination from the final protocol form of the listing of certain associated symptoms such as dizziness, flank pain, or nervousness.

Some important statistics are not presented per se by the authors but can nevertheless be gleaned. Patients were considered cured if they had a postoperative mean diastolic blood pressure of 90 mm Hg or less with at least a 10 mm Hg decrease from the preoperative level, and they were considered improved if their diastolic blood pressure was maintained between 90 and 110 mm Hg and at least a 15% drop. Nonclassifiable patients were those whose preoperative diastolic blood pressures were between 90 and 100 mm Hg or in whom the specific workup failed to demonstrate functional stenosis. Among the atherosclerotic patients, 46% were cured and 17% were improved, while among the fibromuscular hyperplasia patients 58% were cured and 13% were improved. Overall, 51% were cured, 15% were improved, and in 34% the procedures failed, which can be broken down into an overall benefit rate of 63% for atherosclerosis and 80%

for fibromuscular disease, a difference significant at $P < 0.01$. Patients with unilateral disease fared significantly better (70% benefit rate) than patients with bilateral disease (56% benefit rate), $P < 0.02$. Notably, a benefit rate of 80% was achieved in patients with unilateral fibromuscular hyperplasia as opposed to 43% with bilateral disease, exluding unclassified patients and operative mortalities. Considering only those cases which had functionally significant unilateral lesions, 57% were cured and 17% were improved among atherosclerotic patients, while a remarkable 68% cure rate was achieved and an additional 16% were improved among patients with fibromuscular disease. Patients who had functionally significant bilateral stenosis and an anatomically successful procedure had an overall surgical benefit rate of 77% which was comparable to the overall benefit rate of 79% for patients with similarly defined unilateral disease.

The investigators were at a loss to explain why 21% of their best defined surgical candidates were ultimately classified as failures. On the other hand, they emphasized that the incidence of anatomic failure after reconstructive surgery was based only on an analysis of patients who were subjected to postoperative arteriograms, usually because of recurrent hypertension. This would probably skew the reported incidence of failure upwards relative to the true incidence, and they cite other studies (c.f.100) indicating a much lower anatomic failure rate. While the operative mortality varied widely depending on the institution (0 to 21%), it was noted to be highest among patients with atherosclerotic lesions and evidence of coronary artery disease, as well as in patients with bilateral lesions who underwent bilateral procedures. Overall, despite its deficiencies, the Cooperative Study contributed interesting statistics on surgical treatment of renovascular disease.

A recent study that is unique in that only patients with fibromuscular disease were included showed extremely encouraging results of operative treatment in this form of the disease (109). One hundred and thirteen patients were selected on the basis of rapid sequence intravenous urography ($n = 100$), arteriography ($n = 113$), and peripheral PRA ($n = 23$) or renal vein renin ratio ($n = 70$). Regarding arteriography, the authors considered it important to demonstrate functional collateral vessels circumventing a stenosis (defined as narrowing to <1.5 mm diameter); this was done by observing the presence of dilution defects in vessels beyond the stenosis and demonstration of blood flow reversal after infusion of acetylcholine or epinephrine into distal nonparenchymal renal artery branches. Renin ratios of 1.40 or greater were considered to be functionally significant. The patients underwent a total of 158 surgical procedures. Whereas the mean blood pressure at presentation was 210/122 mm Hg and 184/113 mm Hg after medical therapy, (details of drug therapy not presented), after surgical treatment the mean blood pressures were 138/87 mm Hg. This was significantly better regardless of whether or not initial medical therapy had been undertaken ($P < 0.001$). Twenty-five percent of the patients benefited, 62 being cured and 45 significantly improved (normotensive with drugs or diastolic pressure between 90 and 110 mm Hg and 15% lower than preoperative levels). The authors found a significant difference in the surgical success rate between the patients who had demonstrable collateral vessels on arteriography and those who did not ($P < 0.05$). They also found that elevations of the renin index [(individual renal renin activity - systemic renin activity)/ systemic renin activity] correlated well with eventual cure or improvement (96, 97). Furthermore, on the same basis, those two groups could be differentiated from each other; however, there was overlap in the range of values so that categorization of an individual patient using the renin index is not absolute.

More recently, Buda et al reported a series of 116 patients in whom the diagnostic workup included renal vein ratios, peripheral PRA, bilateral renal biopsies at the time of operation ($n = 28$), and saralasin responsiveness ($n = 6$), in addition to rapid sequence IVP, radioisotope renography and renal arteriography (110). Fifty-eight percent of the patients had atherosclerosis and 36% had fibromuscular disease. Overall, 66% were cured surgically and 19% were improved with no operative mortalities; the most successful group was that of unilateral fibromuscular disease, of which 80% were cured and an additional 16% were improved. Patients who demonstrated positive results of IVP, radioisotope renogram, or arteriogram obtained benefit rates of 82, 78, and 84 percent, respectively. Using Vaughan's criteria, at least 90% of patients with positive results of any one of PRA, renin index, or contralateral renin suppression were benefited by surgery (97). When all three determinations were suggestive of functional renal artery stenosis, the benefit rate was 95%; remarkably, these data include atherosclerotic patients as well as those with fibromuscular disease. The renal vein ratio studies were helpful, but 63% of patients with ratios of less than 1.5 benefited from surgery, and there were some false positives as well. Although only six patients were involved in the saralasin-response study, the results were encouraging. The five patients who responded to saralasin with a fall in blood pressure all benefited from surgery, and the one patient whose hypertension was refractory to saralasin also failed to respond to operative treatment.

Indications for Surgery

On the basis of the aforementioned experience with operative treatment, various authors have presented guidelines for choosing surgical candidates. There is general agreement that the outcome of surgery may be highly dependent on careful patient selection.

The specific diagnostic workup plays a critical role. The basic procedure has already been reviewed in Tables I–III, but the question remains how to choose those patients who have not only demonstrable renal artery stenosis, but who also are likely to benefit from surgery. The clinical features of the patient are important, since all of the studies demonstrate superior operative results for those cases where the offending lesion is fibromuscular dysplasia (c.f.104–110) and the preoperative differentiation of this disease from atherosclerosis is a clinical as well as radiologic decision (see Diagnosis). Approximately 90–95 percent of patients in this category will benefit from surgery, and even most of those who advocate basically a medical approach to renovascular disease concede that in these cases surgery should be the prime therapeutic modality (111). The cornerstone of demonstrating a functional lesion after arteriographic demonstration of the stenosis is the renal vein-renin ratio, which is generally of significance when greater than 1.5 (74, 107). However, a few authors have noted that this test alone does not constitute sufficient evidence of a functional stenosis because of the high incidence of false negatives, but instead provides useful corroboration of the arteriogram and IVP (70, 112). As already noted, split renal function tests are no longer considered to be of major value by most authors (70, 84, 85, 97). The rapid sequence IVP when used alone, may also yield an excessive number of false negatives (101). The authors of the Cooperative Study, nevertheless, found that when both the split renal function studies and renal venous renin assays were positive, a beneficial result could be expected in 90% of the cases; however, the tests that today will likely yield the most accurate prediction of surgical success are Vaughan's criteria (97, 101).

In 1973, Vaughan and his associates proposed specific quantitative parameters to test the functional significance of a stenotic lesion and to predict surgical cure. First, they postulated that the reason many investigators failed to consistently correlate high PRA with renovascular hypertension was due to a failure to index the renin value against sodium excretion, based on the demonstration that the clearance rate of renin remains a constant proportion of the arterial renin level (113). Secondly, in extending the analogy of renovascular disease to the two-kidney Goldblatt model, they felt that sustained hypertension should completely suppress renin secretion from the contralateral uninvolved kidney. Therefore, demonstration of a contralateral renal vein renin concentration (V) approaching the arterial concentration (A) would demonstrate this functional property of renal artery stenosis. However, this test is technically challenging so the investigators found a third criterion. They reasoned that as long as the hepatic removal rate remains constant, the renal vein renin increment from the affected kidney must be at least 48% higher than the arterial level. Furthermore, renal plasma flow would bear an inversely proportional relationship with the renal vein renin increment. On this basis, in a pure Goldblatt situation the expression (V - A)/A, or the percent increment in renin from a kidney, must be greater than or equal to forty eight percent. It is pointed out that while each of the three criteria individually may be somewhat unreliable, collectively they constitute a superb predictor of surgical success; a scoring system was devised to weigh the relative importance of each test. In 19 adult patients in whom the scoring system was applied, a surgical cure was correctly predicted in 13 of 13 (100 percent), and a lack of cure was predicted in five of five (100%), while a technical error was identified in one patient. The predictive accuracy of this system was supported by Buda's study in which 116 patients were operated upon and 95% of the patients who fulfilled Vaughan's criteria obtained beneficial results (110). In a more recent publication, Vaughan and Laragh suggest the use of saralasin, propranolol, or converting-enzyme inhibitors to test the renin-angiotensinaldosterone axis when their quantitative criteria yield borderline measurements (114). In this regard, Buda's results with saralasin infusion become all the more interesting and certainly will be the subject of future investigations (110).

Others find that measures can be taken to improve the predictability of various diagnostic tests. Hunt and Strong recommend that the initial tests be postponed until the patient has been off drug therapy for 30 days. The patient is then maintained for three days during which sodium and potassium intake are limited each day to 20 mEq and 90 mEq, respectively, and 1 gm of chlorothiazide is administered daily. They also found it highly desirable to administer atropine before obtaining renin samples (106).

A continuing problem, however, is the evaluation of potential surgical benefits in bilateral disease. Most of the studies cited in this review offer less encouraging operative results in the patients. Foster and his associates concluded that if the renin activity is very high on both sides it should be considered bilaterally significant, and bilateral reconstruction should, therefore, be undertaken (101). In cases with more equivocal renin values, they chose to operate on the side which appeared more stenotic on arteriography, provided the hypertension was severe and refractory to drug therapy; functional tests were then repeated postoperatively if hypertension persisted and further treatment proceeded accordingly. The authors of the Cooperative Study concurred with this general approach, adding that the surgical results in bilateral disease are improved by secondary procedures, as in unilateral disease, when thrombosis of the reconstruction has been arteriographically demonstrated (107).

Other factors in the selection of patients for surgery are other associated manifestations of atherosclerosis, and age. Concerning the latter, most authors proceed with caution when faced with an older patient, and tend to give medical treatment a longer trial, especially now that more specific drug therapy is available (115, 116). However, in a recent review, Dean and Foster conclude that given the high prevalence of renovascular hypertension over age 50 (31%), the low operative risk demonstrated in the more current studies (which they estimate at one to two percent), and the high probability of benefit (80 to 87 percent) with the latest diagnostic approaches, an aggressive attitude towards management is warranted even in an elderly patient provided he is otherwise healthy. They agree with the vast majority of opinion, however, that when there are significant manifestations of atherosclerosis elsewhere, i.e. advanced cardiac or severe cerebrovascular disease, the risks of surgery outweigh the possible benefits (117).

Genest et al add another counterindication to surgery. In their experience, the width of the renal cortex as measured on late renal angiographic films is an important parameter. When this width is decreased to below 5 mm, they claim it is usually indicative of significant arteriosclerosis of the arcuate and interlobular arteries, and they find that surgery fails in almost all these cases (115).

Summary

It has been estimated that the cost of a complete diagnostic workup for renovascular hypertension is approximately $2000 and that the average cost of surgical treatment is $20,000 (118). However, to date there has been no comprehensive study on the management of this disease where the surgical approach was chosen on a purely randomized basis. The earlier reports generally showed the results of surgical management tending to be more successful than medical management, but this might be because the healthier patients were usually the ones selected for surgery. On the other hand, with the recent advent of more specific drug modalities, patients might not be reaching the operating room unless they are medical failures, which would skew the results more towards conservative management. The situation is complicated by the safer and more successful surgery being reported in the more recent studies, in all likelihood due to improved preoperative diagnostic and prognostic techniques; thus, it is even more difficult to compare medical with surgical management on the basis of the entire experience of the past fifteen years (Table VI).

Very few studies have appeared where the same researchers have presented results of both medical and surgical treatment. Such studies that have appeared are often plagued by varying criteria for patient selection (even within a single study), incomplete reporting of patients' characteristics such as the incidence of related cardiovascular symptoms, inadequate patient follow-up, and insufficient reporting of operative complications which should be stratified according to the nature of the disease and the specific procedure used if useful information is to be gained. These deficiencies are also common in publications which deal with either medical or surgical treatment alone.

Despite these difficulties, it is evident that renovascular hypertension is being more precisely diagnosed, and successfully treated both medically and surgically, than in even the recent past. There is every reason to believe this trend will continue as our knowledge of the basic mechanisms underlying this disease grows.

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Hyperparathyroidism with Aberrant Hyperplastic Parathyroid Located within Thyroid Adenoma

WALTER FUTTERWEIT, M.D. AND ARTHUR E. SCHWARTZ, M.D.

The possible ectopic location of parathyroid glands is a challenge faced in every neck exploration for hyperparathyroidism. Not only may one of the usual four glands be found in an ectopic location, but the additional presence of one, two, or even three glands must be considered. The fact that an aberrant parathyroid may lie completely within the thyroid, and thus not be visible at surgery, has gained increased recognition (1). The practical value of this information has contributed to the increasing percentage of initially successful neck explorations for hyperparathyroidism.

We recently saw a patient with primary hyperparathyroidism in whom four hyperplastic parathyroid glands were identified at neck exploration. A pedunculated thyroid adenoma incidentally removed during the procedure was found to contain a fifth hyperplastic parathyroid gland.

Case Report

A 49-year-old man was admitted to The Mount Sinai Hospital with a history of four episodes of renal stones over a fifteen year period. Hypercalcemia with serum calcium levels ranging from 10.5 to 12.5 mg% had been present for two years. Additional history included frequency of urination, back pains, and cramps in the lower extremities.

The pertinent physical findings included generalized obesity, a blood pressure of 134/94 mm Hg, and the presence of a 3.0 cm in diameter soft, circumscribed mass in the area of the superior pole of the left lobe of the thyroid.

RAI-131 thyroid scan disclosed an apparently normal thyroid with absent uptake over the left anterior neck mass. A bone survey demonstrated vertebral demineralization and subperiosteal resorption on the medial aspect of the phalanges. The serum parathormone level was 522 pg percent (normal range is 163–347 pg percent at the patient's serum calcium level of 12.1 mg percent).

The findings at neck exploration are depicted in Fig. 1. Four parathyroid glands were identified in their usual location. A normal sized 3–4 mm right lower gland was not disturbed. An enlarged 5–6 mm right upper gland was removed; the frozen section was reported as an enlarged parathyroid. The left upper and left lower parathyroid glands were 5–6 mm in diameter; two-thirds of each was removed. The remnants of these glands and the remaining right lower gland were labelled with silver clips. A 3.0 cm diameter thyroid adenoma arising from a pedicle in the left superior pole of the thyroid gland and corresponding to the palpable neck mass was incidentally removed. The remaining thyroid gland appeared normal. Frozen section of the thyroid mass was reported as "follicular adenoma with Hurthle cell components."

On final pathologic examination, a fifth parathyroid gland with chief cell hyperplasia was found in the wall of the resected thyroid adenoma (Fig. 2). This had not been recognized at surgery nor on frozen section examination.

Postoperatively, the serum calcium dropped to a level of 9.3 mg percent and has remained in the normal range for the past two years. There have been no further episodes of renal stones.

Discussion

This patient exhibited symptoms consistent with primary hyperparathyroidism and experienced prompt reversal of his hypercalcemia following subtotal parathyroidectomy. Paraffin sections disclosed chief cell hyperplasia in the three removed parathyroid glands, and similar findings in a fifth ectopic gland located within a thyroid adenoma.

From the Division of Endocrinology of the Department of Medicine and the Department of Surgery, Mount Sinai School of Medicine of The City University of New York, New York, N. Y. 10029

Requests for reprints should be sent to: Walter Futterweit, M.D., Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, N. Y. 10029

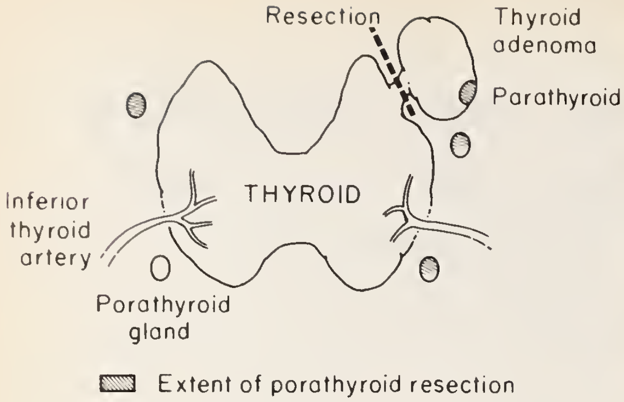

FIG. 1 Diagram of findings at neck exploration.

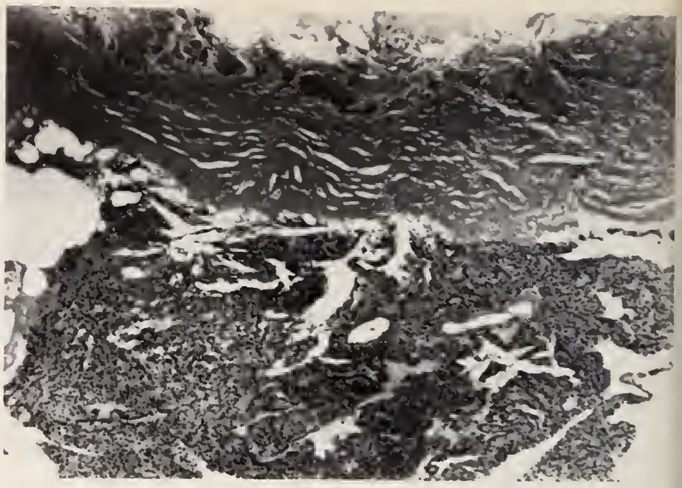

FIG. 2 Chief cell hyperplasia of parathyroid gland located within wall of thyroid adenoma. Low magnification × 60.

The essence of surgery for hyperparathyroidism is the location of abnormal parathyroid glands. In well over 95 percent of cases this can be accomplished through a neck incision. When the parathyroid glands are present in their classic location their identification offers no difficulty. If one or more parathyroid glands are not found in their expected locations, a thorough and orderly search materially increases the chance of success. Vascular pedicles are sought and traced, particularly from the inferior thyroid artery; these often lead to an ectopic gland. A negative search of the lateral neck along the carotid sheath should be followed by removal of the thymus gland through the neck incision. This may yield a parathyroid gland in the anterior mediastinum, sometimes completely embedded within the thymus. If this proves unsuccessful, the areas lateral and posterior to the esophagus should be searched.

The incidence of adenomatous or hyperplastic parathyroid tissue within the thyroid has been reported to be as high as 5–10 percent (1, 2). If a thorough exploration of the neck and superior mediastinum through a cervical incision fails to locate the site of parathyroid pathology or produces only three or fewer glands, we advocate a blind resection of the thyroid lobe on the side of the absent parathyroid gland. The relatively high incidence of parathyroid adenomas and hyperplastic glands within the thyroid makes this procedure a more logical choice than an immediate sternum-splitting exploration of the mediastinum. The morbidity of the operation is reduced, and the yield of ectopic intrathyroidal adenomatous or hyperplastic parathyroid glands has been as great as those recovered by sternal-splitting incisions (3).

In this patient, the removal of an unrecognized additional hyperplastic parathyroid gland located within a thyroid adenoma contributed to the successful management of primary hyperparathyroidism.

Acknowledgment

We gratefully acknowledge the kind referral of this patient by Dr. Leonard Beier, Spring Valley, New York

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Abdominal Pain in the Emergency Room: A Study of 176 Consecutive Cases

JAYNE S. WEISS, B.A., AND ARTHUR H. AUFSES, JR., M.D.

Each year the Department of Surgery of The Mount Sinai Medical Center offers summer fellowships to first- and second-year students in Mount Sinai School of Medicine to work on a research project of their own choosing within the department. During the summer of 1976, one student fellow undertook a prospective study of 176 consecutive cases of abdominal pain seen in the adult emergency room of The Mount Sinai Hospital. The goals of the study were: 1) to determine the cause of abdominal pain in the 176 cases, 2) to follow the 96 patients whose complaint of pain was ascribed to gastrointestinal disease, 3) to determine the efficiency of the emergency room in evaluating abdominal pain, 4) to serve as a learning experience in the diagnosis of abdominal pain.

The study also gave the authors the opportunity to review at close hand, the operation of a large and busy emergency room in a major urban teaching hospital. The data obtained and the conclusions reached form the basis of this report.

Setting

The Mount Sinai Hospital is a voluntary nonprofit institution located in a low socioeconomic neighborhood in New York City. In 1975, visits to the emergency room totaled 59,000, representing a 61.5% increase over the 33,000 visits to the emergency room made in 1970. Because the hospital does not have its own ambulance service, the adult emergency room, which serves patients over 20 years of age, is primarily ambulatory. The percentage of patients arriving via private ambulance is very low.

In the emergency room, the patient registers and is seen by the screening nurse who writes the patient's primary complaint on the chart. After being screened, the patient waits to be seen by a physician.

The adult emergency room is divided into medical and surgical sections, each of which is staffed on a 24-hour basis by first- and second-year postgraduate house officers. Before a patient can be admitted to the hospital, he or she must be seen by a resident physician from the admitting service.

Methods

During the period June 23, 1976 to July 6, 1976, 2,237 patients registered in the adult emergency room. Using the screening nurse's description of the primary complaint, 176 consecutive cases of abdominal pain were selected. These 176 patients were categorized by diagnosis using the following criteria. The impression of the examining physician was used to classify the cause of the complaint into either gastrointestinal (gastroenteritis, cholecystitis, etc.) or nongastrointestinal (gynecological, genitourinary, etc.). When the physician did not list an impression, the patient was classified as gastrointestinal—no diagnosis, if referred to a medical or surgical clinic. If the patients were not referred to either of these clinics but were referred to the gynecology or genitourinary clinic, they were classified as nongastrointestinal-gynecologic or nongastrointestinal-genitourinary, respectively. If the above criteria were unavailable, patients were classified as nongastrointestinal-gynecologic if they were seen by the gynecology resident or complained of abnormal vaginal discharge or bleeding. Remaining patients were classified as gastrointestinal-no diagnosis. Patients with multiple visits were classified using the diagnosis made at the most recent visit. There were two instances where other diagnoses were suggested, diverticulitis or carcinoma of the colon in one patient, and ulcer or obstruction in the second patient. As both diagnoses were gastrointestinal in nature, these patients were categorized as gastrointestinal-no diagnosis. One patient had two diagnoses suggested, pelvic inflammatory disease or diverticulitis. The other patient had the differential diagnosis of either pregnancy or gastroenteritis. Both patients were arbitrarily assigned to the gastrointestinal category; the former diagnosed as diverticulitis and the latter as gastroenteritis.

From the Department of Surgery, Mount Sinai School of Medicine of The City University of New York and The Mount Sinai Hospital, New York, N.Y. 10029

Requests for reprints should be sent to: Arthur H. Aufses, Jr., M.D., Chairman & Franz W. Sichel Professor, Department of Surgery, Mount Sinai School of Medicine of The City University of New York, One Gustave L. Levy Place, New York, N.Y. 10029

Once classified, only patients in the gastrointestinal category were followed for the duration of the study. The initial and final diagnoses of admitted patients were compared. Patients returning home were telephoned the following day. If there was no answer, they were then called at frequent intervals for a period of two weeks in an attempt to contact them. When reached, they were asked if their abdominal pain had ceased, decreased, remained the same, or increased. They were also asked if they were taking any medication for the abdominal pain other than that prescribed in the emergency room, and whether they had seen any other doctors for their pain after leaving the emergency room. On July 7, 1976, a ten-day strike of nonprofessional hospital employees necessitated cancelling most clinic appointments. The charts of these patients were reviewed after one year in order to allow adequate time for appointment rescheduling, appropriate laboratory tests and final diagnosis.

Results

From June 23 to July 6, 1976, 2,237 patients were registered in the adult emergency room. One hundred and seventy-six were examined for abdominal pain. Seven patients were seen twice during the study accounting for 183 patient visits (8.3%). Forty-five percent of the 176 patients had pain due to nonabdominal causes. Gynecologic problems accounted for almost 25% of all complaints of abdominal pain while genitourinary problems accounted for almost 15% (Table I).

In 54.5% of the 176 patients, the cause of pain was classified gastrointestinal, using the previously described criteria. Only these cases were followed further. In 35.4% of these 96 patients there was no diagnosis listed. 26.0% of these patients were diagnosed as gastroenteritis, gall bladder related disease, or hernia. The diagnoses of all cases are listed in Table I.

Follow-up

40.6% of the patients returned home, 37.5% were referred to clinic, and 21.8% were admitted. The mean ages of patients referred to clinic or admitted was 49.5-years-old and 49.6-years-old, respectively. The mean age of patients sent home without further referral was 40.8 years (Table III).

TABLE I
Diagnosis

Diagnosis	Number	% of Nongastrointestinal Patients	% of all Patients
Nongastrointestinal Etiology	80	100%	45.5%
Gynecological	41	51.3	23.3
Genitourinary	26	32.5	14.8
Miscellaneous	13	16.3	7.4
		% of Gastrointestinal Patients	
Gastrointestinal Etiology	96	100%	54.5%
No diagnosis	34	35.4	19.3
Gastroenteritis	9	9.4	5.1
Gallbladder related	8	8.3	4.5
Hernia: inguinal (5) hiatal (2) incisional (1)	8	8.3	4.5
G.I. bleed	4	4.2	2.3
Ulcer	4	4.2	2.3
Appendix related	3	3.1	1.7
Obstruction	3	3.1	1.7
Diverticulitis	3	3.1	1.7
Esophageal reflux	2	2.1	1.1
Pancreatitis	2	2.1	1.1
Hepatitis	2	2.1	1.1
Spastic colitis	2	2.1	1.1
Functional disorder	2	2.1	1.1
Constipation	2	2.1	1.1
Cancer	2	2.1	1.1
Entercolitis	1	1.0	.6
Gastritis	1	1.0	.6
Cirrhosis	1	1.0	.6
Overeating	1	1.0	.6
Postsurgical pain	1	1.0	.6
Postsurgical infection	1	1.0	.6

TABLE II

Flow Chart of Study–June 23–July 6, 1976

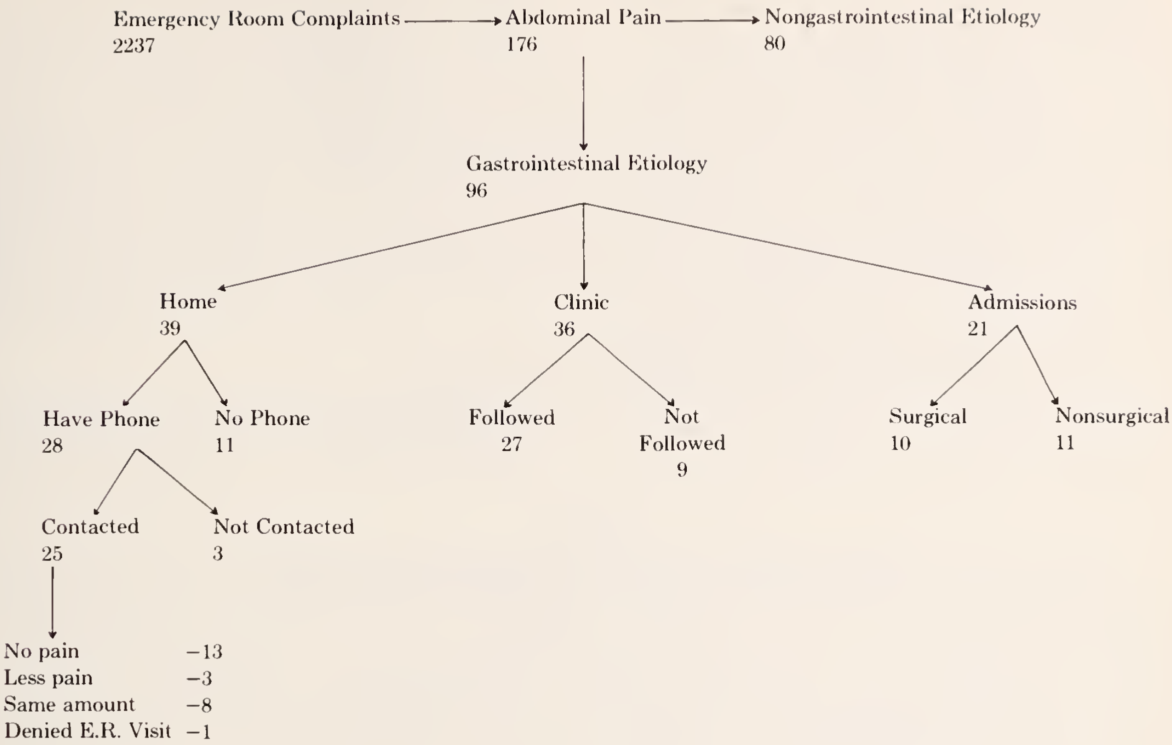

Emergency Room Complaints
2237
Abdominal Pain
176
Nongastrointestinal Etiology
80
Gastrointestinal Etiology
96
Home
39
Clinic
36
Admissions
21
Have Phone
28
No Phone
11
Followed
27
Not Followed
9
Surgical
10
Nonsurgical
11
Contacted
25
Not Contacted
3
No pain −13
Less pain −3
Same amount −8
Denied E.R. Visit −1

TABLE III

Age Distribution

Category	Number	Average Age	Age Range
Home	39	40.8	20–84
Clinic	36	49.5	20–85
Admissions	21	49.6	20–89

TABLE IV

Follow up of Patients Returning Home

Severity of Pain	Number	Percentage	No. of Patients seen by another physician after emergency room visit
No pain	13	52.0%	2
Less pain	3	12.0%	0
Same amount of pain	8	32.0	1
More pain	0	0	0

Eleven (28%) of the 39 patients sent home did not have telephones. Twenty-five (89%) of the remaining 28 patients were contacted by phone. Thirteen (52%) patients no longer had any abdominal pain. Two of these patients (15%) attributed their recovery to another physician that they had seen after visiting the emergency room. One of the patients was diagnosed as having spastic colitis in the emergency room. She subsequently was treated by her own physician for inflammation of the tubes and her pain abated. The other patient was diagnosed as having gastroenteritis. Her own physician treated her for food poisoning, whereupon her symptoms disappeared. Three patients (12%) had less pain after the visit to the emergency room. Eight patients (32%) had the same amount of pain before and after their visit to the emergency room. Of these, one underwent an orchioplasty in another hospital for the pain, two weeks after his visit to our emergency room. We do not know if his pain was relieved by the surgical procedure. One patient denied ever being seen in the emergency room. No patients complained of increased pain after their visit to the emergency room (Table IV).

Thirty-six patients were referred to clinic. The charts of 35 patients were reviewed one year following their emergency room visit, one patient's chart could not be located. Thirteen patients did not attend clinic, 5 of these patients subsequently returned to the hospital with other complaints and no apparent morbidity resulting from their previous abdominal ailment.

Patients that made appointments for clinic before leaving the emergency room were more likely to attend clinic (90%) than those that did not (21%) (Table V).

Of the 22 patients who attended clinic, the etiology of the abdominal pain was undetermined in eight patients after further examination. Five of these eight patients did not keep subsequent clinic appointments. If one assumes that these patients would have received diagnoses had they returned to clinic, the adjusted percentage of patients that could not be diagnosed was 13.590%.

The remaining 14 patients received diagnoses in the clinic. The initial emergency room impression and the clinic diagnosis differed in three cases. One patient complaining of crampy right lower quadrant pain was sent to clinic to rule out chronic cholecystitis, and was diagnosed as having pain secondary to anxiety. Another patient complained of epigastric pain exacerbated by food, was sent to clinic with an initial impression of gallstones and was found to have a duodenal ulcer. A third patient complained of postprandial epigastric discomfort, nausea, constipation, swelling of the ankles after standing for prolonged periods of time, and increased frequency of urination. On physical examination, a mass in his lower left quadrant was palpated, no masses were found on rectal examination. He was found to have a blood urea nitrogen (BUN) of 94 and a creatinine of 10.8. The emergency room diagnosis was "possible cancer." In the clinic, he was found to have chronic renal failure, secondary to prostatic hypertrophy (Table VI).

Of the patients with abdominal pain of abdominal etiology, 21.8% were admitted. Of the 21 patients admitted to the hospital, one died of hepatic and renal failure. The average stay of the 20 patients was 11.8 days. In 20 patients, the diagnosis made in the emergency room agreed with the final diagnosis. One patient admitted with a diagnosis of perforated ulcer, was later proven to have cholecystitis and cholecystectomy was performed. Ten patients (47.6%) had surgical procedures. In all cases the pre and postoperative diagnosis agreed (Table VII).

Return Visits

Two patients initially seen in the emergency room with abdominal complaints two weeks before the inception of

TABLE V

Clinic Attendance vs. Appointments Made in Emergency Room

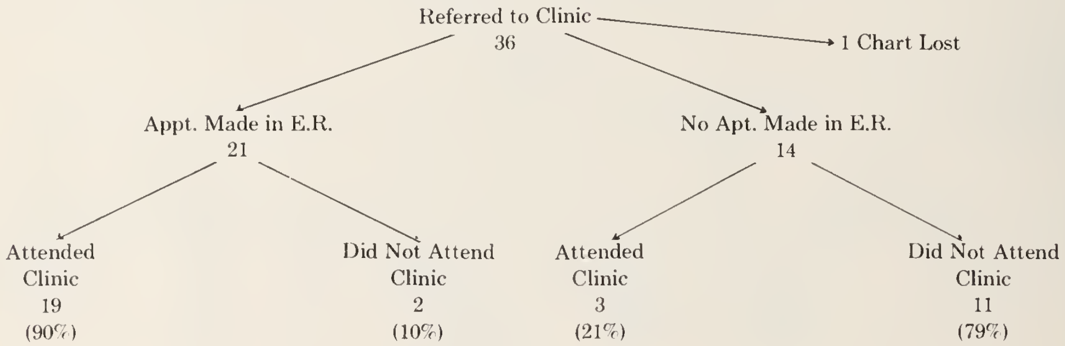

Referred to Clinic
36
1 Chart Lost
Appt. Made in E.R.
21
No Apt. Made in E.R.
14
Attended
Clinic
19
(90%)
Did Not Attend
Clinic
2
(10%)
Attended
Clinic
3
(21%)
Did Not Attend
Clinic
11
(79%)

TABLE VI

Follow-up of Patients Referred to Clinic

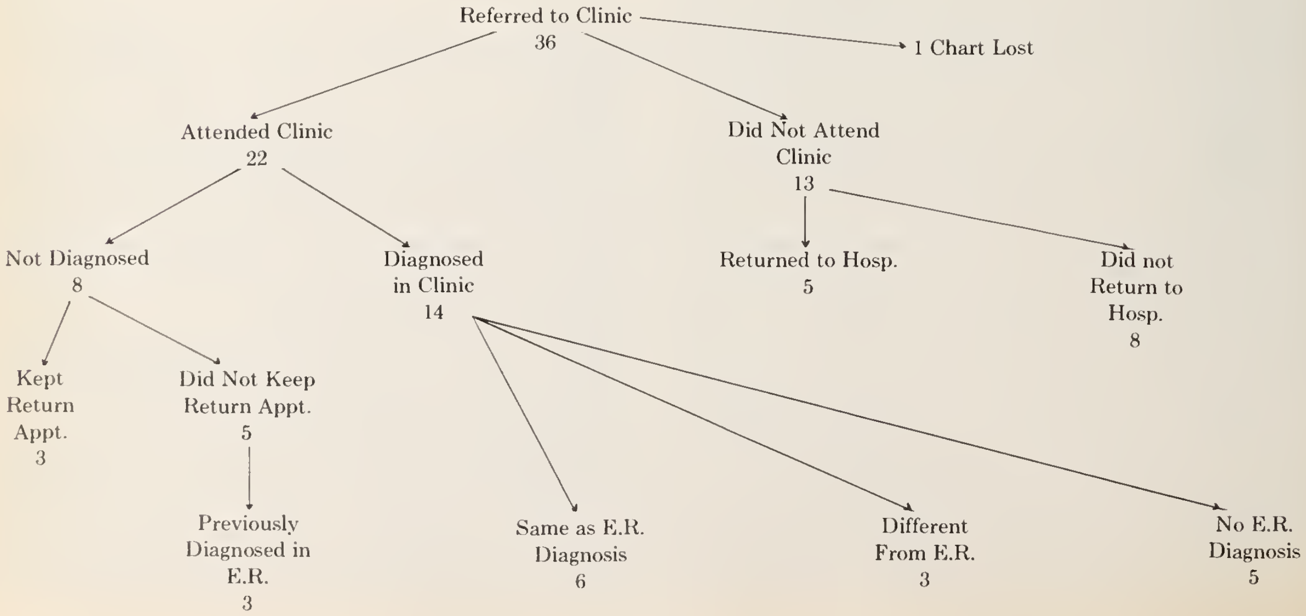

Referred to Clinic
36
1 Chart Lost
Attended Clinic
22
Did Not Attend
Clinic
13
Not Diagnosed
8
Diagnosed
in Clinic
14
Returned to Hosp.
5
Did not
Return to
Hosp.
8
Kept
Return
Appt.
3
Did Not Keep
Return Appt.
5
Previously
Diagnosed in
E.R.
3
Same as E.R.
Diagnosis
6
Different
From E.R.
3
No E.R.
Diagnosis
5

TABLE VII

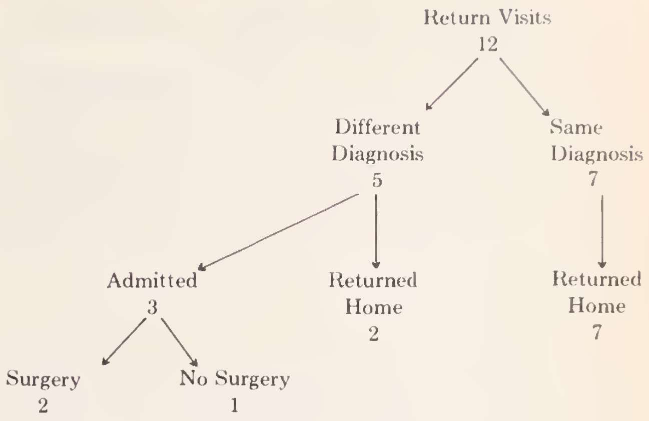
Followup of Admitted Patients

Initial Diagnosis	Number	Surgical Procedure	Number
Appendix related	3	Appendectomy	1
Obstruction	3	Laparotomy Colostomy	1 1
Ulcer	3*	Vagotomy and Pylorostomy	1
Cholecystitis	3*	Cholecystectomy	4*
Hernia Inguinal-1 Incisional-1	2	Herniorraphy	2
G.I. Bleed	2		
Diverticulitis	2		
Pancreatitis	1		
Cirrhosis	1		
Pain secondary to colonic cancer	1		

* One patient admitted with the initial diagnosis of a perforated ulcer, was found to have cholecystitis and a cholecystectomy was performed.

TABLE VIII

Return Visits



this study returned to the emergency room with the same complaint during the course of the study. Ten patients seen in the emergency room during the study returned with the same complaint within a two-week period. Three of these returned to the emergency room after the collection of data was completed. Five of the twelve patients were referred to clinic on their initial emergency room visit (Table VIII).

Three patients were admitted. The first patient had a previous colectomy and ileostomy and complained that "his tube was out of place." His physical examination and laboratory data were within normal limits. He went home but returned to the emergency room the next day and was admitted with a diagnosis of a perforated ulcer. In the hospital, the case was diagnosed as cholecystitis and a cholecystectomy was performed.

In the second case, a patient with a history of gallstones, ulcers and hernia came in with mid-epigastric pain, nausea, vomiting and constipation. He returned the next day with the same symptoms, was admitted, and a cholecystectomy was subsequently performed.

In the third case, the patient had been seen two weeks before with nausea, vomiting, fever, and diarrhea and complained that he had eaten "bad meat." Laboratory data were within normal limits. The patient was told that he had a virus and returned home. Diarrhea and left lower quadrant pain persisted and he was admitted to the hospital two weeks later with a diagnosis of probable diverticulitis. He responded to therapy with ampicillin and was released after a fifteen-day hospital stay.

In two additional cases, the first and second diagnoses disagreed. These patients were not admitted. In one of these cases the examining physician palpated an ill-defined mass in the right lower quadrant and referred the patient to the medical clinic to rule out an appendiceal abscess. The patient returned four days later, at which time the examining physician felt no mass and the new diagnosis was pelvic inflammatory disease.

In the second case, the patient complained of right lower quadrant pain for three days which began on the last day of her menstrual period. The diagnosis was dysmenorrhea. She returned three days later and was examined by the same physician who found her colon to be "full of gas" on physical examination and diagnosed the problem as a functional bowel disorder.

Doctors should be particularly diligent in their examination of returning patients. In 42% (5) of the cases, the first and second diagnosis did not agree. Of patients returning to the emergency room, 25% (3) required admission to the hospital, two being operated upon promptly after admission.

Discussion

The first known study categorizing a large number of emergency room patients with complaints of abdominal pain was reported from the University of Virginia Medical Center (1). They reported that 5% of emergency room visits were due to abdominal complaints. This compares with our figure of 8.3% and a figure of 2.3% for a smaller series of cases studied at the City Hospital Center at Elmhurst by the Health Services Research Unit, Department of Ambulatory Care.

The frequency of distinct gastrointestinal disease entities that we found to be the causal agent of the abdominal pain in emergency room patients was similar to that found in the University of Virginia Medical Center Study (1).

Our study shows that of all patients entering the emergency room with abdominal pain, 55% had probable gastrointestinal disease, although only 35% with abdominal pain were diagnosed as having specific gastrointestinal disease. This indicates that most patients entering the emergency room with complaints of abdominal pain do not have gastrointestinal disease as a primary causal agent. In addition, a large percentage of patients receive no diagnosis in the emergency room.

Of the 96 patients with a diagnosis of gastrointestinal disease, 21 were admitted to the hospital and ten patients had operations performed. We, therefore, concur with previous studies that conclude that the emergency room primarily serves as a 24-hour clinic rather than as an emergency care facility. The vast majority of complaints of abdominal pain in the emergency room were of a nonemergency nature.

An important part of this study was an attempted follow-up of those patients who were sent home. We have tried to measure the successful treatment of the patient who returned home by subjective evaluation of how the patient felt. Difficulties are inherent in using a subjective means to evaluate patient care. Bias is also introduced by only contacting patients with telephones, thus eliminating the lower socioeconomic classes from the follow-up. Of the 25 patients so followed, three subsequently saw another physician whose diagnosis of their abdominal pain differed from that of the emergency room physician.

The diagnosis in 21% of the patients attending clinic differed from the initial emergency room impression.

The number of return visits by patients with abdominal pain can serve to evaluate care given in the emergency room. During the study period, 12 patients made return visits to the emergency room. Of this group, three (25%) were admitted and two were operated upon. A patient who returns to the emergency room after having been previously seen must be presumed to be acutely ill until proven otherwise.

Almost half of our patients who were admitted to the hospital were operated upon. In all cases, the pre- and postoperative diagnoses were the same.

This study demonstrates the need to reevaluate the goals and functions of the emergency room in treatment of the acutely ill patient. Further studies of this type may be useful in evaluating the effectiveness of emergency room procedures.

Summary

Of the 2,237 patients seen in the adult emergency room of The Mount Sinai Hospital during a period of two weeks, 176 consecutive cases of abdominal pain were studied in order to determine the cause of abdominal pain. We then followed 96 patients whose complaint of pain was ascribed to gastrointestinal disease.

Of all patients, 8.3% appeared with abdominal pain. Of these 54.5% had probable gastrointestinal disorder, although only 35.4% of the patients with abdominal pain were given a diagnosis of specific gastrointestinal disease. Many patients received no diagnosis.

Of the patients having probable gastrointestinal disorder, 21.9% were admitted and 47.6% of this group had surgical procedures. Another 37.5% were referred to clinic. The diagnosis in 21% of the patients attending clinic differed from the initial emergency room impression. There were 40.6% patients returned home without further referral. Of these subsequently contacted, 52% no longer had pain, 12% had less pain and 32% reported no change.

Of the 12 patients who returned to the emergency room after being previously examined, 42% received a different diagnosis and 25% were admitted. The returning patient must be presumed to be acutely ill until proven otherwise.

Our study also indicated that the emergency room of The Mount Sinai Hospital primarily serves as a 24-hour clinic.

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Enteroenteric Intussusception in Crohn's Disease

ADRIAN J. GREENSTEIN, M.D., MARTIN WERTKIN, M.D., GEOFFREY DOUGHLIN, M.D., AND ARTHUR SICULAR, M.D.

Intussusception in the adult is a relatively uncommon cause of intestinal obstruction. This contrasts with intussusception in infants in which ileocecal intussusception occurring in the first and second years of life is one of the more common causes of intestinal obstruction. Whereas the cause of the intussusception is unexplained in as many as 95% of infants, in 40% of adult intussusception an organic cause may be recognized with 80% of such cases being related to benign or malignant tumors (1). We have, within the last three years, seen two patients whose postoperative jejunojejunal intussusception occurred in the postoperative period following distal small bowel resection for Crohn's disease. Each patient had dilated bowel related to previous intestinal obstruction and had developed the obstruction following surgery. Each patient had had a long tube in position prior to the obstructing episode. Both were successfully operated on, the intussusception reduced without resection, and in each case, the results have been salutory.

History

Case #1. This 52-year-old male patient was admitted with a 30-year history of intermittent diarrhea, initially diagnosed as a regional enteritis but subsequently found to be caused by granulomatous ileocolitis. The early period was characterized by abdominal pain and diarrhea; and ten years after the onset of the symptoms, the patient developed an ileosigmoid fistula. This was characterized by continuous diarrhea of five to six watery bowel movements per day. In the early years, he had bloody bowel movements; but subsequently, although the diarrhea persisted, the bowel movements were nonbloody. He also had a history of polyarthritis of a migratory nature with episodic swelling of his ankles, pain, and fever. Just prior to his admission to The Mount Sinai Hospital in 1975, he had several episodes of obstruction that were relieved by the passage of stools. Ultimately, he progressed to complete obstruction associated with vomiting and abdominal distension. A long tube was inserted with decompression of his abdomen. However, in view of the prolonged history and progressively increased narrowing of the rectosigmoid region, associated with an ileosigmoid fistula, surgery was advised.

At laparotomy he was found to have extensive disease of the distal ileum and proximal cecum. In addition, there was a fistula from the ileum to the midsigmoid, and the sigmoid was diseased from the middle third, down to the upper third of the rectum. The lower sigmoid and rectosigmoid were extremely narrowed and the obvious site of the progressive intestinal obstruction. The actual site of fistula in the ileum was approximately 60 cm proximal to the severe disease in the distal ileum. The disease involved the proximal four inches of the cecum and the distal ileum. An ileocecal resection with ileoascending colostomy at the midascending colon was carried out. This was followed by an anterior resection with a coloproctostomy to the slightly diseased upper third of the rectum. To decompress the two distal anastomoses, the small bowel was brought out at the fistula site as a loop ileostomy. Thus, the obvious danger of closing a relatively normal ileum at the fistula site, proximal to an ileocolic and colocolic anastomosis, was obviated. Pathology revealed transmural colitis with ulceration and pseudopolyp formation but without granulomata. The histopathology of the ulcerated small bowel was characteristic of transmural inflammatory disease but without granulomata. However, the small bowel at the site of the fistula resected at the time of closure of the ileostomy, did, in fact, contain granulomas further confirming the diagnosis of inflammatory bowel disease.

The first postoperative week was uncomplicated. The Cantor tube was removed and the patient was started on clear fluids. Following this, his ileostomy output steadily increased in volume from approximately 2000 cc to as much as 4000 cc/24 hr. This steadily increasing volume was felt to be due to an incomplete obstruction in the small bowel proximal to the lesion, but initial x-ray failed

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From the Department of Surgery, Mount Sinai School of Medicine of The City University of New York and The Mount Sinai Hospital, New York, N.Y. 10029.

Requests for reprints should be sent to: Adrian J. Greenstein, M.D. Department of Surgery, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, N.Y. 10029.

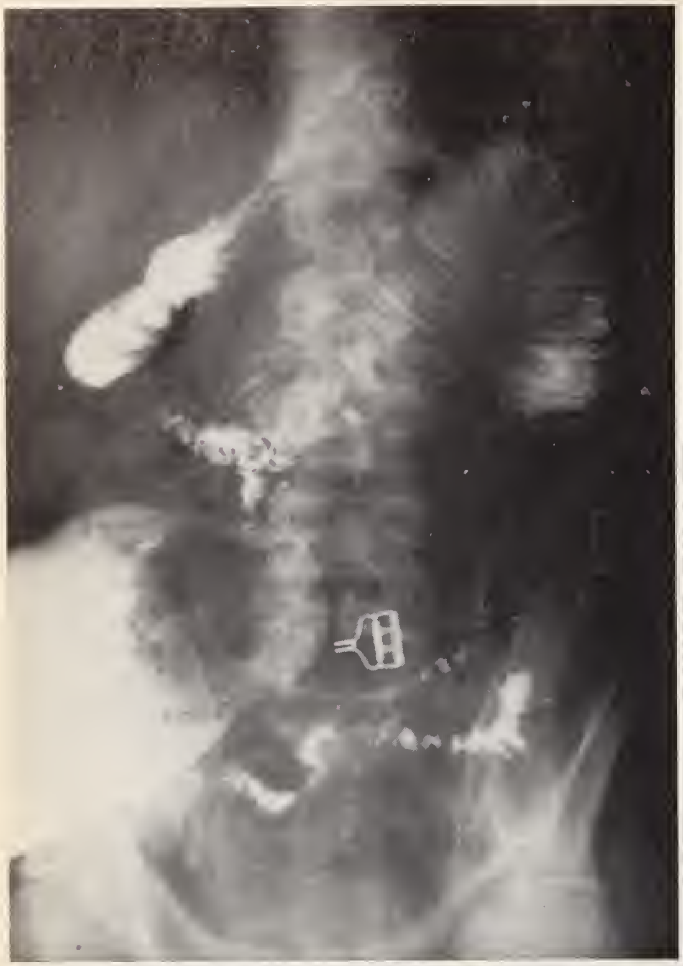

FIG. 1: Small bowel series on patient #1 showing sharp cut off of upper jejunum with dilated proximal small bowel.

to demonstrate a clear cut lesion. Ultimately, one month after the first operation when a sharp cut-off was demonstrated in the proximal jejunum, the patient was taken back to the operating room with the objective of closing the loop ileostomy and dealing with any obstruction should this be found proximally (Fig. 1). At the time of laparotomy, an intussusception of eight inches of jejunum, in an antegrade fashion into the loop immediately distal to it, was found at a site 12 inches from the ligament of Treitz. This was reduced with great difficulty by Pope's method (2). In the described method, the little finger is inserted into the neck of the intussusception and adhesions binding the entering and turning layers are broken down. This was followed by gradual reduction of the intussusception by blunt and sharp dissection. The bowel proximal to the site of the intussusception was approximately two and one-half inches in diameter, extremely dilated, and even more so at the site of the intussusception itself. The distal bowel was relatively collapsed. In a retrospective review of the initial postoperative x-ray, the site of the intussusception was recognized (Fig. 2).

Following closure of the ileostomy and reduction of the intussusception, the patient recovered well from surgery, and his postoperative course since has been uncomplicated. He is now, two years following this procedure, in good health with little significant symptomatology and no residual diarrhea.

Case #2: A 31-year-old lawyer was admitted to hospital with an 18-month history of diarrhea, weight loss of forty pounds, and the diagnosis of granulomatous enteritis involving the distal small bowel. He was treated unsuccessfully with prednisone for one month. Subsequent treatment with azulfidine produced a minimal response with some amelioration of his symptoms. His history revealed an episode of intestinal obstruction as an infant, successfully treated by laparotomy with resection of a Meckel's diverticulum. Following this, he developed multiple perirectal abscesses and fistulae which were drained in subsequent years. This hospital admission was prompted by exacerbation of his symptoms, including fever, diarrhea and abdominal pain. Examination revealed a tender mass in the right lower quadrant. He was treated with antibiotics for a week but developed abdominal distension. Barium enema and small bowel series revealed a stricture of the distal two feet of ileum,

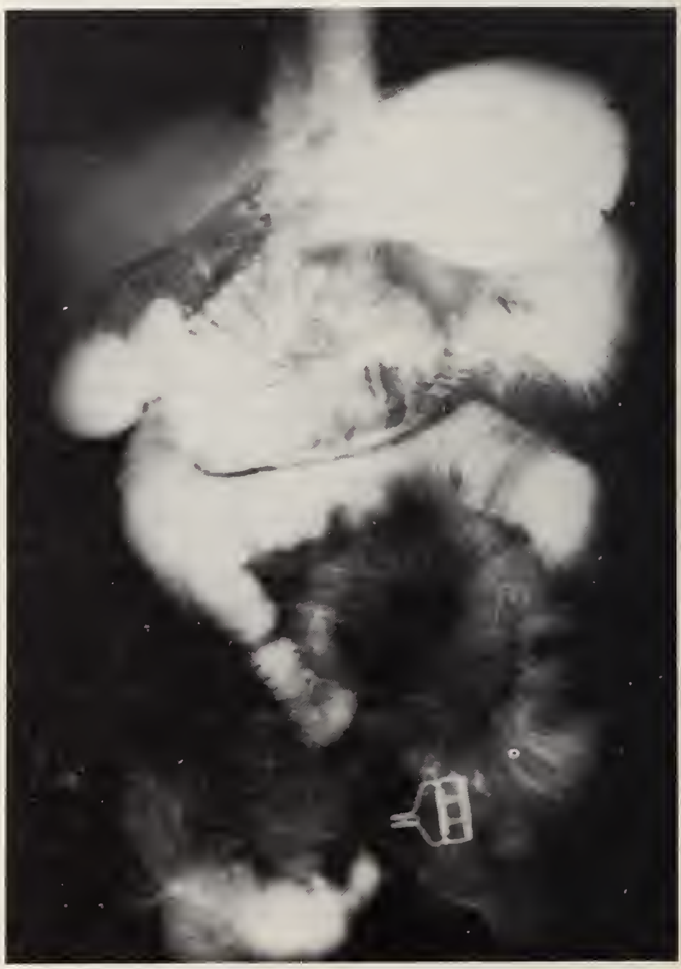

FIG. 2: Small bowel series on patient #1 showing site of intussusception as a filling defect in upper jejunum.

proximal small bowel distension, and fistula formation around the cecum. He underwent laparotomy which revealed mesenteric thickening with massive lymphadenopathy displacing both the sigmoid colon and bladder. The mass originated in the diseased terminal ileum and ileosigmoid. Several ileocecal fistulae were found. The Cantor tube was advanced to within one foot of the diseased distal ileum, and a primary ileocecal resection and ileoascending colostomy was performed. Although the postoperative course was somewhat slow, it was otherwise unremarkable. The Cantor tube was removed on the eighth postoperative day. He was soon able to tolerate a normal diet and was discharged completely asymptomatic one week later. Pathology confirmed the presence of granulomatous enteritis with fistulae.

The patient was readmitted six weeks later with severe, crampy, left upper quadrant pain. Examination on readmission revealed visible peristalsis in the upper abdomen. Auscultation revealed a loud bruit to the right of the paramedian incision. Small bowel series demonstrated proximal small bowel obstruction, and angiography confirmed the diagnosis of an arteriovenous fistula in the jejunal mesentery. Emergency laparotomy revealed the unexpected finding of a jejunojejunal intussusception with fibrous and fibrinous adhesions binding the intussusceptum to the covering intestine (Fig. 3). In addition, the presence of an arteriovenous fistula in the jejunal mesentery was confirmed and this lesion was resected. Since the patient had already had two previous resections of small bowel, a prolonged, tedious effort was made to reduce the intussuscepted segment of bowel, and this was finally successful. The intussusceptum was beefy red and thickened but it was still clearly viable. Thus, we elected not to resect but to preserve this dilated bowel which was now fixed in its reduced position by an edematous mesentery. The postoperative course was once again uncomplicated and he was discharged two weeks following surgery. Two months after this conservative procedure the patient is well without evidence of further obstruction. Postoperative review of the emergency gastrointestinal series demonstrates both the intussusception and the point of obstruction immediately proximal to this, without evidence of apparent enteritis or colitis (Fig. 4).

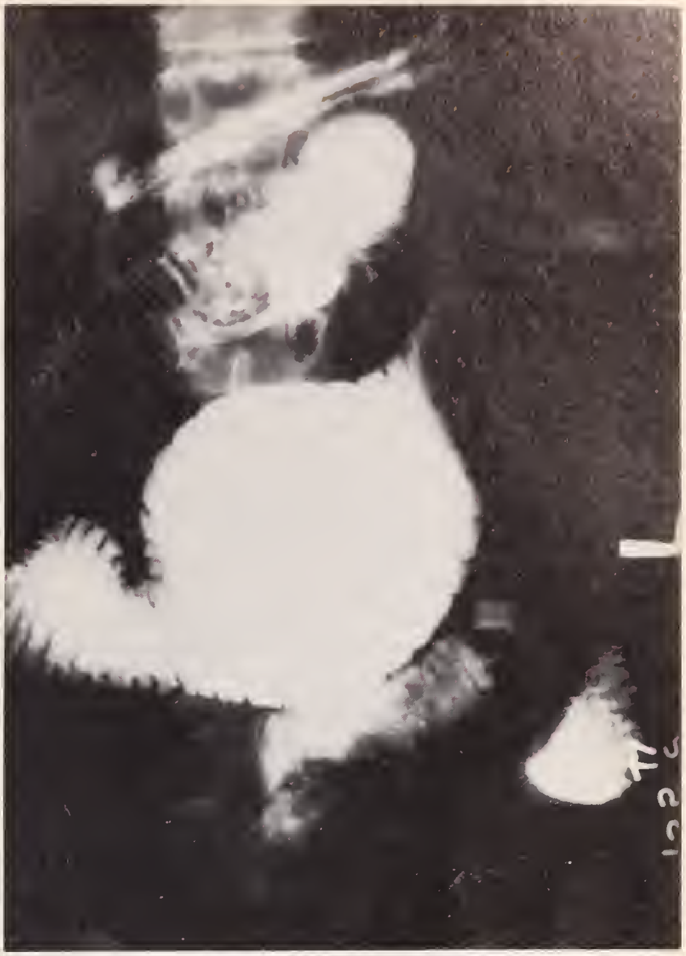

FIG. 4: Preoperative small bowel series showing intussusception and point of obstruction of patient #2.

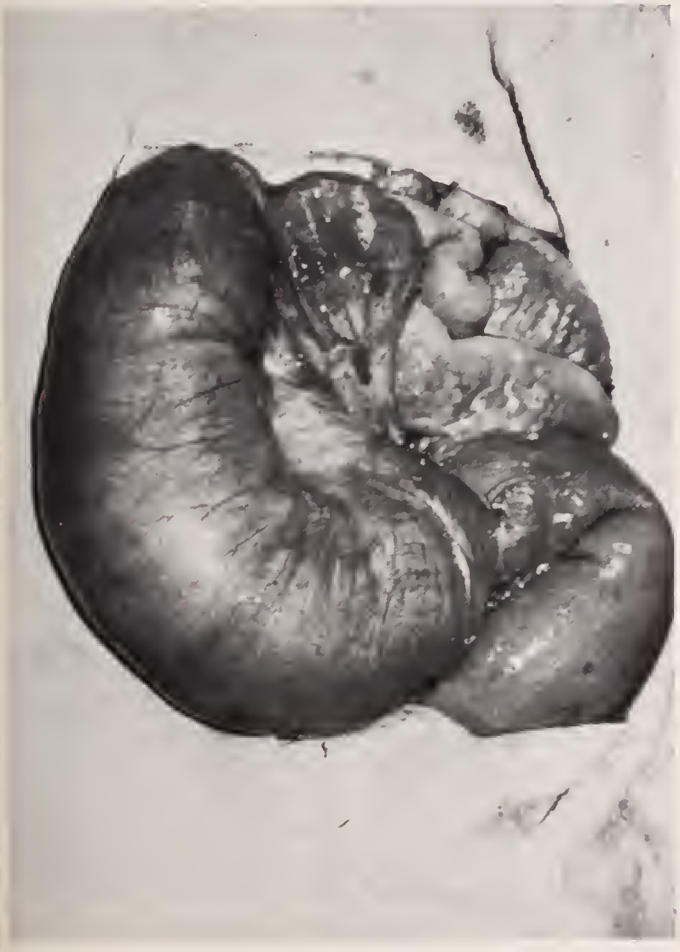

FIG. 3: Photograph of intussuscepted segment of jejunum of patient #2 showing markedly dilated small bowel.

Discussion

Intussusception is a relatively common cause of postoperative intestinal obstruction in children (3–5). Twelve percent of such intestinal obstructions are due to intussusception. In adults, it is rare, both as a cause of intestinal obstruction and as a postoperative complication. Felix et al described a patient with postoperative intussusception following resection of an intussuscepting Burkitt's lymphoma (6). Ginsburg and Friedman described three cases of delayed postoperative intussusception occurring within two months of right hemicolectomy (two cases) and lysis of adhesions (7). Each was antegrade, each followed removal of a long intestinal tube, and each occurred in proximal small bowel within five feet of the ligament of Treitz, as a jejunojejunal intussusception. In each instance, a resection and reanastomosis was required because of inability to completely reduce the intussusception.

In both patients described in this report, a long tube was used for a short period of time. After a period of one, and three months respectively, each patient developed partial subacute intestinal obstruction, manifested by increasing ileostomy output in case #1, and by high, small bowel obstruction in case #2.

The difficulty of preoperatively diagnosing the presence of an intussusception has been stressed previously (8, 9). In each patient the diagnosis of intussusception was made at laparotomy. In both cases, the site of obstruction and the actual intussuscepting segment could be seen on careful review of the small bowel series. The diagnosis should be suspected in the postoperative patient following intubation with a long tube, particularly in obstructing Crohn's disease with dilated proximal small bowel. Although a development of intussusception followed the use of a long tube in each instance, the basic pathologic lesion developed in the presence of a significantly dilated nondiseased small bowel. This resulted from long-standing, chronic, distal intestinal obstruction because of inflammatory bowel disease. In case #1, the intussusception was antegrade and clearly not due to withdrawal of the tube although it may have developed at the time that the tube was in position in the early postoperative period. The interesting feature of this particular case was the minimal amount of pain experienced by this patient as the considerably dilated small bowel allowed for partial obstruction only and for continued passage of fluid bile and pancreatic juices through the obstruction. This patient, in fact, had an overflow secretory state rather than the complete obstruction and vomiting that occurred in patient #2. Studies carried out by Shields on the physiology of intestinal obstruction show that in the early stages of obstruction the secretion of fluid of the obstructed segment is increased considerably (10). The high volume ileostomy output rising to 4000 cc in this patient is consistent with this finding.

It is well recognized that in the postoperative period, a sign of an obstructing intestinal lesion may be high volume output, rather than diminished distal output, progressive distention, and vomiting that are the usual cardinal features of intestinal obstruction. It may be argued that the high output was related directly to the inflammatory bowel disease. It is possible that the grossly distended, proximal small bowel did in fact secrete larger amounts of fluid once it was decompressed. However, the progressive rise in fluid output over the three week period from removal of the tube until the time of reoperation, suggests that this was not the major mechanism but that the progressive luminal narrowing at the site of the intestinal obstruction was the primary cause of the progressively increasing ileostomy output. Furthermore, the satisfactory long-term result excluded widespread ileitis.

We were able gradually to reduce the intussusception completely in each instance with complete resolution of the problem for two years, in one patient, and for a period of months in the second patient. Numerous fibrous adhesions between the intussusception and the intussuscipiens make this a long and tedious dissection utilizing Pope's method described by G. Qvist (2). Because of the importance of preserving as much of the small bowel as possible in Crohn's disease, and because of the previous resection of diseased ileum, we felt that further resection of bowel in these patients was contraindicated. We were able to successfully preserve the somewhat tattered but intact segment of bowel following reduction.

The earliest papers describing adult intussusception, including those of Donhauser and Kelly in 1950, and Roper in 1956, recommended manual reduction prior to resection as the preferred surgical method (11, 12). It has since been appreciated that there is a high rate of malignancy in small bowel, 24 percent, as well as large bowel, 56 percent, intussusception (13, 14). As a result, primary resection without reduction has been recommended as the treatment of choice for all types of adult intussusception (13, 14). We agree with these authors that the increasing appreciation of a malignant lesion as the leading point of the intussusception warrants a more radical resection. This is particularly important as various authors have pointed out that tumor embolization results from manipulation of malignant lesion (15, 16). There are, however, certain exceptions to this rule. One exception to this radical curative surgical approach is the postoperative patient in whom the intussusception is related to the mechanical factors inherent in the use of a long tube. Another is the postraumatic intussusception following a direct blow to the abdomen or severe physical exertion, of which Leichtenstern found 26 of 376 cases, eight percent (17). Furthermore, although development of cancer in both excluded and incontinuity small bowel has been recognized with increased frequency in recent years, this development is uncommon in macroscopically normal bowel particularly if no mass is palpable at laparotomy (18, 19). If the long duration of disease suggests this possibility, particular care should be taken at laparotomy to palpate carefully the reduced segment of small bowel (19).

In Crohn's disease, there are several factors which may predispose to the development of intussusception. These factors include the use of a long intestinal tube, prestenotic dilation of the small bowel, and hypermotility of the remaining short segment following resection of distal small bowel. A gradual but progressive increase in ileostomy volume output in the postoperative period should lead one to suspect an obstructing lesion. In the presence of the above factors, the development of intussusception should be considered in the preoperative evaluation of the patient and early laparotomy and reduction of the intussuscepted segment carried out.

Summary

Two patients with Crohn's disease of an obstructing type developed postoperative jejunojejunal intussusception. The obstructing episodes, within three weeks, and two months after surgery, respectively, followed removal of a long intestinal tube. The patients were different. One had complete obstruction, distension and vomiting. The other had partial obstruction and high volume ileostomy output distal to the intussusception.

Both patients were satisfactorily treated by reoperation and disinvagination of the intussuscepted segment without resection. In both instances, the procedure was difficult and tedious because of the formation of adhesions between the intussusceptum and the intussuscepiens. The immediate and long-term results have been satisfactory in the two patients, six months later and again two years later, following the operative procedures.

We recommend this conservative approach with careful mechanical disinvagination of the intussusception whenever possible in postoperative jejunojejunal intussusception following distal resection for Crohn's disease. Preservation of small bowel is of particular importance in Crohn's disease to avoid the long-term risk of short bowel syndrome, while the risk of cancer in incontinuity normal bowel is relatively low. A high index of suspicion will lead to early diagnosis and exploration before compromise of bowel.

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Correlation of HPL and Total Estrogen in Complicated Pregnancies and the Influence of Maternal Weight on HPL Result

James McCarrick, M.S., Jasmin Moshirpur, M.D., Ezra Levy, Ph.D., and Jona Allerhand, M.D.

Obstetricians, unlike other physicians, are caring for two patients simultaneously, mother and fetus. The mother is readily available for examination but the fetus is relatively inaccessible. The health conditions of the mother obviously influence the fetus (1). The concept of the fetal-placental unit was introduced to study the mutual relationship of the mother and the intrauterine status of the fetus (2–5). Many biochemical and biophysical tests were evaluated for the assessment of the fetal development in relation to normal fetal growth, fetal well-being, and the determination of fetal maturity (5–8). To date, there are no ideal tests in existence that reflect the intrauterine well-being of the fetus as related to the placenta and maternal physiology (1).

Among the various biochemical tests, enzymatic and hormonal, proposed for the monitoring of pregnancy, the determinations of maternal estrogen and HPL (human placental lactogen) levels have gained general acceptance (1, 9–11). The determinations of total urinary estrogen and of free estriol in serum have been shown to correlate well, making either test comparable (12, 13). Nevertheless, controversial opinions exist regarding the clinical value of these tests (4, 14–18).

The aim of this study was to compare the results of maternal total urinary estrogen and blood HPL as indicators of fetal well-being in complicated pregnancies. The determinations were started from the third trimester and the outcomes of the pregnancies were recorded.

Taking into account only those patients that had multiple determinations, three groups could be distinguished (19). The largest group (GI) had acceptable normal third trimester values for both hormones and presented the least number of complications at delivery. A relatively small group (GII) showed persistent low values for both tests and had the highest rate of complications. A significant group (GIII) of patients maintained normal total urinary estrogen levels but had low HPL levels. This group exhibited an intermediate rate of complications.

Retrospectively, it was also found that there was a statistically significant number of obese women in GIII with an initial weight of over 160 pounds ($P < .001$).

No case of placental sulfatase deficiency as demonstrated by low total estrogen content and normal HPL levels was found in this study (20).

Materials and Methods

The current study comprised 321 pregnant women that were in the third trimester. The reasons for HPL and total urinary estrogen evaluation were based on previous medical or obstetric history and/or specific problems related to the current pregnancy (Table I). Thirty-one cases were excluded from the final evaluation because of incomplete record data. Of the remaining 290 cases, 87 were primiparas and 203, multiparas. Table II illustrates the distribution of the two groups by age.

Whenever a 24-hour total urinary estrogen level was requested, a serum HPL was also drawn. This resulted in 1319 comparative determinations averaging 4.5 matched samples per patient.

Total urinary estrogens were determined by a modified Kober reaction (21). All specimens were run in duplicate. A patient specimen from the previous run was repeated as part of a quality control program. Results were accepted if the standard error was less than 10% ($N = 95$, $2.2 \pm 8.7\%$). Concentrations above 10 mg/24 hr were considered normal for the third trimester by this method.

HPL levels were measured in duplicate by radioimmunoassay (Pharmacia Diagnostics, N.J.). A commercial control serum (Phadebas Reference Serum) having a mean value of 4 μg/ml was included in every run. The

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From the Department of Laboratories and the Department of Obstetrics and Gynecology, Mount Sinai School of Medicine (CUNY), Mount Sinai Services, The City Hospital Center at Elmhurst, New York, N.Y. 11373.

Requests for reprints should be sent to Dr. Jasmin Moshirpur, Department of Obstetrics and Gynecology, The City Hospital Center at Elmhurst, 79-01 Broadway, Elmhurst, N.Y. 11373.

TABLE I

Clinical Indications for Test Performance

Clinical History	Diabetes (a)	Preeclampsia Hypertensive	Vascular Disease	Miscarriage or Stillborn	Irregular menses	C/S (b)	IGR (c)	EDC (d)	Post Due	Weight Gain
Previous	38	5-Pre. 1-Hyp.	22	19 Mis. 11 Still	26	20				
Current	60 A 1 B	18-Pre. 3-Hyp.					10	24	80	3

a. white classification
b. cesarean section
c. intrauterine growth retardation
d. estimated date of confinement

TABLE II

*Distribution by Age, Parity and Initial Weight**

Age Groups	15–20	21–24	25–28	29–32	33–36	37–40
number of patients	47	78	68	57	23	17
primi-gravida	19	30	23	7	4	4
weight at initial visit 160 lb	8	14	26	16	3	6

* Prenatal care usually initiated at 16 weeks.

laboratory mean was 4.0 ± 0.2 (N = 54). Values over 4 μg/ml after 30 weeks were accepted as normal.

Results

Figure 1 shows typical results obtained from the total urinary estrogens and HPL determinations. The normal rise in both tests can be seen up to about the 36th week of gestation.

Analysis of the results from 290 patients revealed three groups as illustrated in Table III. GI consisted of 232 cases where both hormonal parameters were within the normal limits for the third trimester. This group showed the lowest incidence of complications, 11 cases (4.7%). One of the deaths included in this group was probably due to a tight cord around the baby's neck during delivery.

GII was composed of 14 cases where both determinations were below normal. This group showed the highest number of complicated pregnancies, 10 out of 14 cases (71.4%). The major complications of this group included three deaths and seven babies with birth weights below 2500 gm.

GIII consisted of 44 patients who had normal third trimester levels of total urinary estrogens but whose HPL levels remained consistently below 4 μg/ml. Fifteen of this group (34.1%) had complications.

It can also be seen in Table III that 50% of the pregnant mothers in GIII had initial weights of 160 lb or over at the first clinic visit which generally occurred during the sixteenth week of gestation.

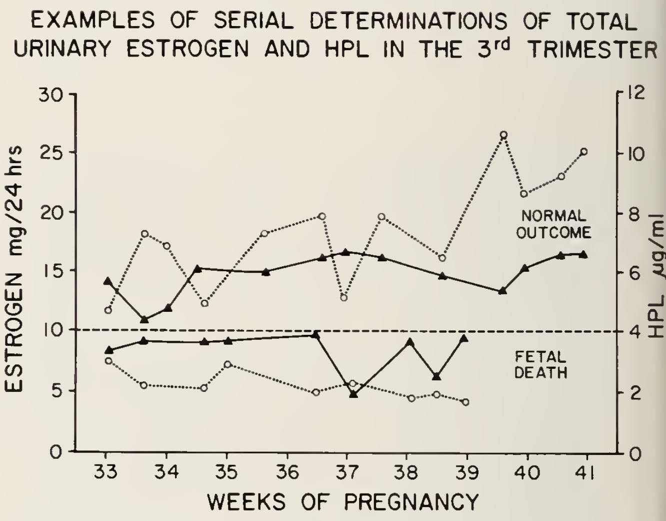

FIG. 1. Levels above the dotted line indicate accepted normal values for the third trimester.

Discussion

Two conclusions can be reached by analyzing the results of this study. The first concerns the sensitivity of serum HPL determinations as an indicator of pregnancies at risk followed during the third trimester. The second refers to the finding that low HPL values in mothers with normal total urinary estrogens during the studied period were often associated with increased maternal weights, i.e., over 160 lb, at the onset of pregnancies 50% in GIII, 20.7% and 21.4% respectively in GI and GII. This difference is of statistical significance (P < .001) (Table II).

The concept of the fetal-placental unit as an integrated endocrine entity was introduced by Diczfalusy (2). It was demonstrated that steroid production of this unit is accomplished by enzymatic systems present in either the fetus or placenta so that mutual interaction is needed. On this basis, total estrogen determinations have been used for the assessment of fetal well-being.

Though HPL was discovered in 1962 by Josimovich and McLaren, the complete biologic effects of HPL still remain to be determined (22, 23). It is produced in the

TABLE III

Results of Hormone Assays Related to Initial Mothers' Weight and the Newborn

Estrogen (E) (mg/24 hr) vs HPL (μg/ml)	Number of Cases	Mothers' weight 160 lb	Neonatal Deaths	Newborns 2500 g	Low Apgar Cyanosis Mec. Stain Resp. Dist.	Birth Defects	Cases with Complications
GI E>10 HPL>4	232	48 (20.7%)	3	4	4	0	11 (4.7%)
GII E<10 HPL<4	14	3 (21.4%)	3	7	3	1	10 (71.4%)
GIII E>10 HPL<4	44	22 (50%)	2	6	7	6	15 (34.1%)

placenta by the syncytiotrophoblast and excreted directly into the maternal circulation, with only 1% found in the fetus. It is considered to be an indicator of fetal development that depends on placental function (10, 15). It is known to increase the production of free fatty acids, and decrease blood glucose by increasing insulin concentration (10, 23). HPL has been shown to restore the secretory function of the pancreas for insulin in hypophysectomized rats (24). Although the importance of HPL concentration as an indicator of fetal-placental function still remains controversial, recent studies have repeatedly shown that values below 4 μg/ml occur in only 1–2% of normal pregnancies. Values below this level have been described by Spellacy et al as the fetal danger zone (F-D zone) (14). In general, repeated low concentrations of HPL have been associated with high risk pregnancies such as maternal vascular diseases, fetal growth retardation, complications during delivery, and even intelligence impairment of the newborn (5, 16).

The mechanism of HPL action is unknown, but the short half-life of between 10–30 min in the maternal circulation enhances its ability to reflect rapid change in placental integrity and consequently fetal well-being. Therefore, only serial determinations are of prognostic value (5, 18, 25).

Retrospectively, as shown in Table III, obesity was common in 50% of mothers in GIII, where normal total estrogen levels were found, but the HPL levels were in the F-D zone. This group showed an intermediate number of pregnancy complications, 34.1%, when compared to GII, 71.4%, and GI, 4.7%. This phenomenon perhaps could be explained by taking into account the recent data of hormonal activity regarding the mode of biologic function (26, 27). It was shown that there are two types of hormonal activity. Steroid and thyroid hormones, which are water soluble, freely permeate the membrane and interact with specific binding proteins of receptors in the cytoplasm and nucleus of the cell. In contrast, polypeptide hormones first bind to specific receptor sites on the plasma membrane of the cell. These membrane receptors serve to recognize and bind the specific hormones, and the formed complex activates an "effector" system within the cell. Thus, the peptide hormones can regulate the metabolic processes of a cell without entering it.

Obesity creates a hormonal resistance. An obese person, for example, may have a normal fasting blood glucose level but achieves this only by maintaining insulin levels two to three times larger than normal. The defect was shown to be at the target cell level. Obese persons have impaired binding of I_{125} insulin, and diet can influence this stage. When obese patients were given a low calorie diet for several weeks, the insulin resistance disappeared and the receptor concentration rose to normal. Obesity could have a similar influence on HPL regulation and activity. Both polypeptide hormones are connected with carbohydrate metabolism. A common biologic mechanism can be postulated. A more detailed study on metabolic clearance rates could clarify the correlation between obesity and HPL metabolism (28).

Summary

Results of total urinary estrogen and HPL determinations in the third trimester were compared in 290 complicated pregnancies. According to the hormonal concentrations, three groups could be differentiated: GI, GII, and GIII. In the group in which normal urinary estrogen and low HPL concentrations were obtained (GIII), retrospectively it was found that 50% of the pregnant women were obese with a weight over 160 lb at the onset of pregnancy.

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The Student's Corner

PAUL CELANO, B.A., EDITOR

This column is a forum for medical students to comment on issues concerning medicine, medical school, and medical education. The editor of this column is a second-year medical student and elected student representative at Mount Sinai School of Medicine of The City University of New York. Mount Sinai School of Medicine students are invited to take advantage of this opportunity to reach a wide and influential readership. Medical students from other schools are also invited to contribute.

Contact Mr. Celano through Mount Sinai School of Medicine, Annenberg Building, Room 13-98A, One Gustave L. Levy Place, New York, N.Y. 10029. If you do not have time to write an entire column, you still may contact Mr. Celano and share your thoughts on a particular topic that perhaps can be incorporated into a future column.

David A. Dreiling, M.D.
Editor-in-Chief

Pathophysiology of Pulmonary Fibrosis Occurring in Association with the Adult Respiratory Distress Syndrome

Marc S. Mondschein, B.A.

Introduction

Since its description in 1967, the Adult Respiratory Distress Syndrome (ARDS) has been recognized as a significant cause of death (1). The estimated annual incidence is at least 150,000; of these, fifty percent are not salvageable, which is ample evidence of the vital importance of this condition (2). Although many etiologic factors contribute to ARDS, the clinical course is characterized by the rapid development of pulmonary insufficiency leading to asystole (3). The histopathologic changes are likewise stereotypic with an exudative phase characterized by hyaline membrane production, followed by a proliferative phase marked by pulmonary interstitial fibrosis. Hill et al have noted that "the development of fibrosis is the single biggest common denominator of a poor prognosis" (4). This paper considers the current knowledge of the pathophysiology of acute pulmonary fibrosis as it relates to the ARDS. An exhaustive review of all contributing factors has been avoided; instead, an attempt has been made to clarify common mechanisms.

Historical Perspective

Diffuse pulmonary fibrosis probably finds one of its earliest descriptions in Corrigan's "On Cirrhosis of the Lungs" in 1838 (5). However, modern awareness did not come until 1935 when four cases of "fulminating diffuse interstitial fibrosis" were described by Hamman and Rich (6). This entity was recognized as destinctive because of its unrecognized histologic features coupled with the absence of a known etiology, and because of the rapid clinical course. The rarity of the syndrome is evidenced by the fact that only one more case was described subsequent to a second paper by Hamman and Rich on the subject in 1944 (7). More recent studies associating alveolar septal fibrosis, interstitial round cell inflammation, alveolar desquamation of cells, and hyperplasia of alveolar lining cells with a progressive disease elapsing over a number of years, has resulted in a modification of the original concept of the condition as acute (8). The Hamman-Rich Syndrome is now regarded as identical to Scadding's Fibrosing Alveolitis, Liebow's Usual Interstitial Pneumonia (UIP), and Crystal's Idiopathic Pulmonary Fibrosis (9–11). Peabody et al further amended the syndrome as having three phases: acute fulminating,

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From Mount Sinai School of Medicine, New York, N.Y. 10029. Mr. Mondschein is a fourth year medical student.

subacute, and chronic (12). The acute form has been well described (13–16).

Pulmonary Fibrosis

Response to Injury. Despite its great internal surface area and exposure to a multitude of injuries, the lung is remarkably stereotyped in its response. Although the reaction is similar, the target tissue may differ from different insults; lesions of the endothelium are initially noted in oxygen toxicity, while epithelial injury occurs in the respiratory distress of burn patients (17). Following any of the numerous antecedents of the ARDS such as pulmonary infection, sepsis, hemorrhage, aspiration, trauma, and acute pancreatitis, the lung initially demonstrates an exudative phase in which fluid passes into the interstitium and then into alveolar spaces with the formation of hyaline membranes (18). Without resolution, the inflammation becomes proliferative or reparative with type II alveolar cell hyperplasia, mononuclear cell invasion, and the onset of fibrosis. Experimentally induced oxygen toxicity, judged by Liebow to be the best model of UIP, sometimes results in focal fibrosis by the third day, and extensive interstitial fibrosis after eight days (10, 19). The inspiration of 40% oxygen at atmospheric pressure for as little as three days may cause permanent fibrosis in man (20).

Type II Pneumocyte. The type II, surfactant producing, pneumocyte plays a central role in the response to injury (21). It is not only more resistant to oxidant stress than the type I cell, but is also able to undergo mitosis and transformation to a type I cell, thereby repeating normal embryology (22). After desquamation of necrotic type I cells, that normally line 90% of the alveolus, the type II cells proliferate and become hypertrophic, thus preserving alveolar architecture. Since the type II cells are able to produce collagen, fibrosis may be a nonspecific consequence of their proliferation (23).

Intraalveolar Process. The alveolar exudate is the result of increased pulmonary capillary permeability, increased alveolar epithelial permeability, or abnormalities in the removal of pulmonary fluid (24). Disruption of the alveolar epithelium which normally offers the main resistance to fluid transport across the alveolar-capillary junction leads to alveolar flooding (25). The alveolar exudate contains fibrin that may serve as a stimulant and scaffold for fibroblast proliferation (26). The intraalveolar collagen subsequently produced may be covered by alveolar epithelium and be incorporated into the interstitium, thereby resulting in interstitial fibrosis.

Connective Tissue of the Lung. Pulmonary fibrosis represents both a qualitative and a quantitative alteration of lung connective tissue. Collagen normally comprises 15% to 20% of the total tissue mass, and 60% to 70% of the total connective tissue of the lung (27). The lung is distinctive in possessing the four known types of collagen and thus the five types of alpha chains (27). Three alpha chains interweave to form the tropocollagen helix, which is the building block of collagen. The interstitial network is composed of types I and III collagen, the former having high tensile strength, being found in bone and tendon, and the latter being more flexible. Fibroblasts, type I and II alveolar cells, and smooth muscle cells have the capacity to secrete tropocollagen, while alveolar macrophages do not. In the kitten lung, heavy bands of collagen line the terminal airways and alveolar ducts, and send out appendages that terminate in the adventitia of neighboring blood vessels; finer fibers form an interalveolar network and become incorporated into the alveolar basement membrane (28). Mesenchymal cells and collagen always occupy a central connective tissue sheet within the interalveolar septum; they are normally conspicuously absent from that surface of the capillary that bulges into the alveolus (29).

Sayer et al have noted an absolute increase in collagen in fibrotic lungs with a relative decrease in type III and increase in type I (30). Collagen from control lungs was about 31% type III, while that from fibrotic lungs was 12% to 24% type III. This is consistent with the clinically observed loss of pulmonary compliance in interstitial lung disease. Lysine hydroxylation of the alpha chains of both types may also be reduced. Since hydroxylysyl derivatives serve as sites of inter- and intramolecular crosslinkage, this reduction may result in instability, disorganization, and consequent atypical exposure of lung collagen to the immune system.

Surprisingly, Fulmer and Crystal found that the amount of collagen per dry weight in fibrotic lungs was actually less than that in controls (31). This is partially due to the increased cellularity of the diseased lungs. They emphasize the critical placement of collagen, rather than its diffuse increase in the pathogenesis of the condition. The finding of asymetric interposition of collagen, lymphocytes, macrophages, fibroblasts, and occasional plasma cells within the interalveolar septae with a reduction of pulmonary capillaries in fibrotic lungs supports this hypothesis (32). The interstitial fibrosis associated with bleomycin therapy has a peribronchial and perivascular, as well as a septal distribution (33).

Studies of Pickrell et al suggest that an alteration in collagen turnover may result in fibrosis (34). Exposure of beagles to radionucleotides caused an initial increase in pulmonary collagen breakdown, followed by a more significant increase in collagen synthesis that resulted in its net accumulation. Crystal found that during the first month after birth, the total collagen of rabbit lungs increased five fold, and its concentration doubled (35). In contrast, the compensatory growth of the remaining lung following pneumonectomy in an adult is characterized by a net increase in collagen without a change in concentration. It may be that variable genetically determined regulatory mechanisms function at different periods of life and may become inappropriately operative in pathologic states.

There has been no reported alteration in the Elastin of fibrotic lungs despite its established role in the maintenance of pulmonary elastic recoil (36).

Immunologic Considerations. Interstitial pulmonary fibrosis has been associated with rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, and polymyositis (37–40). This association suggests immunologically mediated mechanisms, that are also suggested by the finding of positive macroglobulins and latex fixation tests in a significant number of patients with idiopathic pulmonary fibrosis (41).

Collagen is highly antigenic. This may be related to the repetitive $(Gly\text{-}X\text{-}Y)_n$ framework of the alpha chains. When native type I collagen, heat denatured collagen, or constituent $alpha_1$ or $alpha_2$ chains are injected subcutaneously in guinea pigs with Freund's complete adjuvant, a cell mediated (type IV) response is evoked (42). A characteristic picture of delayed inflammation with numerous lymphocytes and macrophages becomes maximal by the twentieth day and lasts for a number of months. The immunodominant antigenic determinant has been localized to the nonhelical N-terminal regions of the alpha chains, with that of the $alpha_2$ chain being of particular importance (43). The capacity of collagen to evoke a humoral response is demonstrated by the finding of anticollagen antibodies in the serum and joint fluid of patients with rheumatoid arthritis and chronic joint trauma (44).

Kravis et al found that lymphocytes from 17 out of 18 patients with idiopathic pulmonary fibrosis released macrophage inhibitory factor, a marker of cell-mediated immunity, upon exposure to both type I collagen and the constituent $alpha_1$ and $alpha_2$ chains (45). In contrast, lymphocytes from controls did not have this activity. The patients' lymphocytes also showed cytotoxicity in response to collagen, as demonstrated by the release of ^{51}Cr from collagen-coated sheep red blood cells after the addition of the patients' lymphocytes. This immune response is mediated by T lymphocytes. A collagen activated immune system may be damaging only to the lung because 1) the structure of pulmonary collagen is changed, 2) the lung's collagen is presented to the immune system abnormally, or 3) there is an abnormal lymphocyte-macrophage interaction or loss of suppressor T-cells (45).

A number of observations have suggested a role for the humoral response: 1) Antilung antibody has been shown to stimulate reticulin or collagen-rich hyaline thickening of the interalveolar septa (46). 2) Rabbits with radiation-induced pulmonary fibrosis have elevated gamma globulins (47). 3) Lymphocytes and plasma cells are prominent and closely associated with areas of interstitial fibrosis in bleomycin-induced lung disease (33).

Recent investigations suggest a role for immune complexes in the development of interstitial fibrosis similar to that operating in certain of the glomerulonephritides. Brentjens et al. caused a membranous and/or proliferative pneumonitis in rabbits by evoking a hyperacute antibody response to injections of bovine serum albumin (48). Antibody-antigen-complement complexes were deposited in the alveolar capillary walls and sometimes associated with capillary wall thickening and interstitial fibrosis. Patients with cellular interstitial disease tend to have elevated circulating complexes, while those with markedly fibrotic lungs usually lack them (49). Eisenberg et al found most patients with acute interstitial pneumonitides (e.g. pneumocystis carinii pneumonitis) to have course granular deposits of IgG, IgM, and IgA with complement throughout the interstitium, while few with chronic diffuse fibrosis had such deposition. Thus, immune complexes may initiate the fibrotic process, but be absent from the end-stage scarred organ.

Populations of differing HLA type show variable degrees of fibrosis in response to a similar fibrogenic stimulus. Types HLA-12 and HLA-29 are found in greater frequency in patients with idiopathic pulmonary fibrosis than would be expected by chance (11). 27% of 22 asbestos workers with alleged asbestosis had HLA-27 type compared with 9.8% of controls (51). The familial clustering of idiopathic pulmonary fibrosis also lends support to the concept that genetically determined factors play a role in predisposition to fibrosis (11).

Cellular Mechanisms. Ultimately, the fibroblastic deposition of collagen is regulated by cells with macrophages being of key importance. Most of the macrophages at the site of inflammation and wound repair are derived from monocytes mobilized from the bone marrow, while a minority are tissue macrophages (52). The administration of steroids, which causes a sequestration of peripheral monocytes, and antimacrophage serum results in a marked reduction in the number of fibroblasts at a site of wound repair. Those fibroblasts present, however, appear to be undergoing normal collagen synthesis (52). It has been hypothesized that macrophages control the onset and rate of fibroblast proliferation by the production of a stimulating factor or by the removal of an inhibitor. The supernatant derived from the culture of macrophages exposed to silica promotes collagen synthesis in fibroblast cultures (53). This effect may be mediated by lysosomal enzymes, for all fibrogenic crystals, such as silica, are capable of inducing lysosomal membrane rupture, while nonfibrogenic ones cause little (54).

Macrophages also play a role in immune mechanisms. They are necessary mediators of the fibrotic response to antilung antibodies and are also probably important in the development of cell mediated immunity by processing and presenting the antigenic collagen to T lymphocytes (46, 55). The activated lymphocytes release such lymphokines as chemotactic factors for monocytes and fibroblasts, macrophage activating factor, and macrophage inhibiting factor. Purified T lymphocytes stimulated by phytohemagglutinin, require macrophages in order to produce the fibroblast chemotactic factor (56). Thus, both fibroblasts and macrophages are attracted to the same site, where the latter may stimulate the proliferation and collagen synthesis of the former.

Collagen and its collagenase breakdown products exert monocyte chemotaxis (56). Its failure to have this effect in nonpathologic states may be due to a physiologic sequestration, perhaps imposed by the native architecture of tightly bound fibers encased in the proteoglycan ground substance (57). This organization may be disrupted by various insults, with the collagen consequently exposed to collagenases released from alveolar macrophages and polymorphonuclear leukocytes. The breakdown products may attract monocytes that transform into macrophages and cause fibrosis as discussed above. Hook et al demonstrated a marked inhibition of corneal collagenase after the addition of proteoglycans to collagen in vitro (58). Their observations are consistent with this hypothesis.

The qualitative alterations in the types of collagen present in fibrotic lungs may be related to variability in the specificity of different intrinsic collagenases. While fibroblast and pulmonary alveolar macrophage collagenases destroy types I and III collagen equally, granulocytic collagenase selectively digests type I relative to type III (59). The different collagenases also show variable responses to inhibitors (60).

Proteases such as trypsin, plasmin, and thrombin have been found to release cultured fibroblasts from contact inhibition and stimulate their proliferation (61). Similar enzymes may be released by granulocytes and macrophages during the acute phase of inflammation. The former cells are sequestered in the lungs of shock-induced animals (62). Castor et al have studied a connective tissue activating peptide that is thought to arise from necrotic tissue cells and white blood cells, and is thought to stimulate the metabolic activity and proliferation of connective tissue cells (63). It would thus serve as a link between the exudative and proliferative phases of inflammation. This activation is believed to be mediated via the stimulation of fibroblast adenyl cyclase with resultant increase in intracellular cyclic AMP; it is potentiated by prostaglandin E (64).

Platelets, which are deposited as microthrombi in the shock lungs of ARDS, also release a factor that promotes fibroblast mitosis (65). Pulmonary obstruction secondary to thrombocytic bronchoconstrictors may damage arteriolar walls and thereby contribute to pulmonary edema (66).

Functional Sequelae and Prognosis

Pulmonary fibrosis results in the restrictive sequelae of decreased compliance, decreased total lung capacity, decreased residual volume, decreased diffusion capacity, and increased one minute forced expiratory volume relative to vital capacity. The lower diffusion capacity is secondary to a loss or dysfunction of alveoli rather than to an "alveolar-capillary block" (67). The pressure-volume curve is shifted down and to the right with the maximal static transpulmonary pressure correlating best with the degree of fibrosis (11). A less prominent obstructive component is secondary to peribronchiolar fibrosis (67). These effects can be devastating in the face of the ARDS. Lamy et al found that ARDS patients with a moderate amount of exudate, edema, and hemorrhage usually showed a marked increase in shunt flow in response to decreasing the concentration of inspired oxygen (FiO_2) and a rapid and striking improvement with positive end-expiratory pressure (PEEP), while those patients with significant fibrosis showed a less impressive change in shunt with alteration in FiO_2 and a slow response to PEEP (68). The latter group had a higher incidence of bronchopleural fistulae, as well as a much worse prognosis with 85% of those patients with significant fibrosis expiring.

Most, if not all, survivors of ARDS probably have some residual fibrosis (69). Klein et al found that of eight survivors of ARDS most had some degree of restrictive sequelae (70). Patients with residual defects tend to be among the older age groups (71). Glauser and Smith present the case of a near drowned patient exposed to high levels of oxygen, who on the twelfth day had pulmonary function tests demonstrative of severe restrictive disease—and a lung biopsy showing pulmonary fibrosis, but who had marked improvement in pulmonary function by the fiftieth day (72). Kapanci et al, in studying the sequelae of oxygen toxicity in monkeys, found the restriction imposed by septal scarring and thickening was associated with an increase in the capillary surface area and a doubling of the capillary blood volume (73). Thus while pulmonary fibrosis is permanent, there may be compensatory alterations in pulmonary function that ameliorate its pathophysiologic sequelae.

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BRONX VETERANS ADMINISTRATION MEDICAL CENTER

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Bronx Veterans Administration Medical Center

Introduction

The Bronx Veterans Administration Medical Center had ties with The Mount Sinai Hospital long before Mount Sinai School of Medicine was established and long before the formal affiliation of the two in 1968. Mount Sinai's Dr. Alexander S. Gutman was chairman of our research committee for many years and was a guiding influence in the development of what was soon to become an internationally famous research program. Dr. Hans Popper was and still is an active consultant to the Bronx VA pathology service.

The hospital opened on April 17, 1922 as a psychiatric institution but became a general hospital in 1931. The original buildings were purchased in 1921 from a Roman Catholic orphanage. In 1940, two buildings—a twelve-story center unit and a six-floor administrative complex—were added and the hospital, with 1649 beds, became the second largest Veterans Hospital in the country. As additional Veterans Hospitals were constructed in the New York metropolitan area, the number of beds at the Bronx VA declined.

Today, the medical center awaits its move into its new facilities scheduled for the spring of 1979. The 702-bed hospital, constructed at a cost of over one hundred million dollars, will have the most modern facilities and the latest "state of the art" equipment of any VA Hospital in the country and of any hospital in the City of New York. Each ward unit will have one-, two- or four-bed patient rooms, with classrooms and demonstration rooms for resident and student teaching. Attached to the main building on three floors will be a 50,000 square foot research building. Master plans call for the construction of another 50,000 square foot research unit and a 120-bed nursing home facility in the future.

Residency programs were started in 1945 with the post-World War II reorganization of the Veterans Administration. The hospital became a major resource for training returning World War II physicians. Graduates since then, numbering in the thousands, have become deans and department chairmen and many hold professorial appointments in medical schools throughout the country. The late Solomon Berson, the first Rosenberg Professor and Chairman of Medicine at Mount Sinai School of Medicine, had been a resident here. Dr. Gutman, when Director of Medicine at The Mount Sinai Hospital, would send his future chief residents to the Bronx for one year of training. Dr. Alvin Tierstein was another who went on to a Chief Residency at Mount Sinai and eventually became a professor and a division head.

Currently, there are four independent residency training programs and eleven programs intergrated with The Mount Sinai Hospital residencies. There are affiliations with more than 50 cooperating universities and colleges to provide clinical experience in a variety of allied health fields.

Overshadowing the hospital's long history of excellence in patient care and education has been the accomplishments of its clinical investigators. From the beginning in 1946, research was considered an integral part of patient care and education programs. The story of Dr. Berson and Dr. Rosalyn Yalow in developing radioimmunoassay and exploiting this technique into new frontiers of knowledge in diabetes and other areas of endocrinology and gastroenterology is well known to the Mount Sinai family. Their accomplishments were crowned when the Nobel Laureate in Medicine or Physiology was awarded to Dr. Yalow in 1977. Dr. Ludwik Gross in 1951 discovered the virus, now named after him, which produced murine leukemia. His work reopened the path for the studies in oncogenic vires. He has been honored in the past year by the German and French governments for his discoveries and the subsequent impact on cancer research. Both Dr. Gross and Dr. Yalow have won the Lasker Awards and been elected to the National Academy of Sciences.

There have been many other important contributions from the Bronx staff. The internal arteriovenous fistula which made chronic hemodialysis feasible was developed here by Drs. Jack Cimino and Ken Appel. In Europe, it has been called the "Bronx Shunt." The Middleton Award, given annually by the Veterans Administration for outstanding achievements in research, has been won five times by Bronx investigators. This record far surpasses all VA Hospitals except one, that has been so honored twice. All five awardees are still at the medical center.

In 1979, when the newly renamed Bronx VA Medical Center moves into its ultramodern facilities, its staff does so with the knowledge that much has been accomplished in the old, soon to be demolished building, and we hope that the future will be as bright as the new structure.

Julius Wolf, M.D

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Gastrin and Secretin Radioimmunoassay in Diagnosis and Therapy of Acid-Peptic Disease

EUGENE STRAUS, M.D., ROBERT J. GREENSTEIN, M.D., AND ROSALYN S. YALOW, PH.D

Introduction

The interplay of hormones and target organs in the gastroduodenal-pancreatic axis is crucial in regulating the luminal milieu of the upper gastrointestinal tract. Measurements of the hormones involved are now feasible and make possible improved clinical insight concerning hypergastrinemic-hyperchlorhydric states. The cases reported here illustrate the application of studies of gastrin-secretin hormonal relationships to the diagnostic differentiation and medical management of Zollinger-Ellison syndrome (ZE) and nontumorous hypergastrinemic hyperchlorhydria (NTHH). These approaches are of increasing importance as earlier diagnosis alters the clinical presentation in ZE and H_2-receptor blocking drugs offer a real alternative to surgical therapy.

Materials and Methods

The diagnostic work-up during hospitalization of each of the patients included determination of plasma gastrin before and after a standard test meal (STM) consisting of two hard boiled eggs, toast, and 120 ml of orange juice and before and after a secretin challenge (intravenous administration of Boots or GIH secretin). Plasma secretin was determined in samples obtained before and after feeding and other testing. Hormonal concentrations were determined according to methods commonly used in this laboratory (1–4). The minimal detectable concentrations of these hormones in the assays employed were five picogram (pg) gastrin/ml and twenty pg secretin/ml plasma.

Patient SB. A 75-year-old man was referred to The Mount Sinai Hospital because of diarrhea and weight loss over an 18-month period. During this time, the patient had approximately three to five watery bowel movements per day. Radiologic examination of the upper gastrointestinal tract revealed duodenal scarring. No ulcer crater was seen. Sonography demonstrated a 4 × 4 × 3 cm mass in the head of the pancreas. After an overnight fast, the stomach was emptied with a sump tube and a nasogastric tube was positioned with the aid of fluoroscopy in the most dependent portion of the stomach. Basal acid output (BAO) was measured by hand aspiration of gastric juice over four consecutive 15-minute periods. Each sample was titrated to pH 7 with 0.01 M NaOH. BAO was taken as the mean of the two highest values. The maximum acid output (MAO) was then determined after intramuscular injection of 1.6 mg betazole hydrochloride (Histalog) per kg body weight. Additional gastric analyses were performed similarly with the modification of taking plasma samples before and after clamping the nasogastric tube for specified periods. Gastric analyses were also performed on three successive days beginning at 5.5 hours after the patient had eaten a standard test meal (STM) along with 300, 600, and 900 mg of cimetidine respectively.

Patient AC. A 50-year-old man was admitted to the Bronx Veterans Administration (VA) Medical Center during an episode of hematemesis. Emergency endoscopy revealed a bleeding ulcer. The patient had been taking 200 mg of aspirin per day as treatment for rheumatoid arthritis. The patient's condition stabilized within 48 hours after initiation of nasogastric suction and initiation of cimetidine therapy (300 mg P.O. q6h). The patient received six units of packed red blood cells during this period. Cimetidine therapy was continued but melena developed on the 16th hospital day. Repeat endoscopy demonstrated the source of bleeding to be a new gastric ulcer. Bleeding again abated after 48 hrs of nasogastric suction. Efforts to determine BAO and MAO were unsuccessful due to continuous bile contamination of the gastrin juice which, nevertheless, had a pH of 1.8.

From the Veterans Administration Medical Center, Bronx, N. Y. 10468 and Mount Sinai School of Medicine, The City University of New York, New York, N. Y. 10029.

Requests for reprints should be sent to Dr. Rosalyn S. Yalow, Veterans Administration Medical Center, 130 W. Kingsbridge Road, Bronx, N. Y. 10468.

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Results

Plasma gastrin concentrations before and in response to feeding and secretin challenges are shown in Figure 1. Both patients had fasting hypergastrinemia. Plasma gastrin in patient AC, increased from a fasting level of about 300 pg/ml to almost 700 pg/ml at 20 minutes after completion of the STM. There was no significant change in plasma gastrin following the secretin challenge (Fig. 1, left). In contrast, the basal gastrin concentration of 500–600 pg/ml in patient SB was unchanged during the STM but increased about 300 pg/ml within five minutes following secretin injection (Fig. 1, right). The patterns of gastrin responses are strikingly different; those of AC are characteristic of a patient with hyperactivity of the G-cells of the gastrointestinal mucosa (NTHH), and those of SB are characteristic of ZE (5, 6).

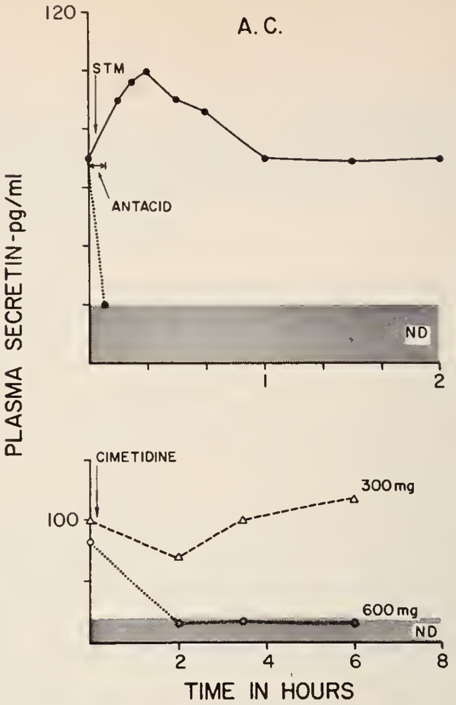

FIG. 2. Plasma secretin in patient AC before and after a STM (●——●) and before and after 80 ml of Mylanta II (top). Plasma secretin before and after administration of cimetidine (bottom). Secretin concentrations below 20 pg/ml are not detectable (ND).

We have previously observed that in most normal subjects and duodenal ulcer patients with BAO <10 mEq/hr, plasma secretin is undetectable in the fasting state (<20 pg/ml) (7). Plasma secretin in patient AC was elevated (70 pg/ml) in the basal state, increased to 100 pg/ml at 20 minutes following the STM and, on another day, was suppressed to undetectable levels very rapidly following ingestion of 80 ml of Mylanta II (Fig. 2, top). Although definitive acid studies could not be performed because of contamination of gastric juice with bile, we interpret these observations as being consistent with basal hyperacidity promoting basal hypersecretinemia. The increased plasma secretin during the STM was probably due to a marked acid response to feeding. The buffering action of the antacid resulted in suppression of plasma secretin. The cimetidine dose (300 mg, q6h), that did not prevent development of a new ulcer, was insufficient to suppress gastric acidity since the secretin level was only slightly decreased even two hours after 300 mg cimetidine. However, plasma secretin was still undetectable at six hours after a 600 mg dose (Fig. 2, bottom). This larger dose evidently had an adequate suppressive effect on gastric acidity since the gastric and duodenal ulcers healed within two weeks on this dosage (q6h) and there has not been a further incident of ulceration over a two-month period.

Fasting plasma secretin in SB averaged about 150–200 pg/ml. Plasma secretin was completely suppressed at one hour following the STM and doses of cimetidine ranged from 300 mg to 900 mg (Fig. 3). However, the largest dose was necessary to suppress plasma secretin for the entire six-hour period. Acid studies at the end of this period demonstrated that there was inadequate suppression by the smaller doses since the acid output had returned to

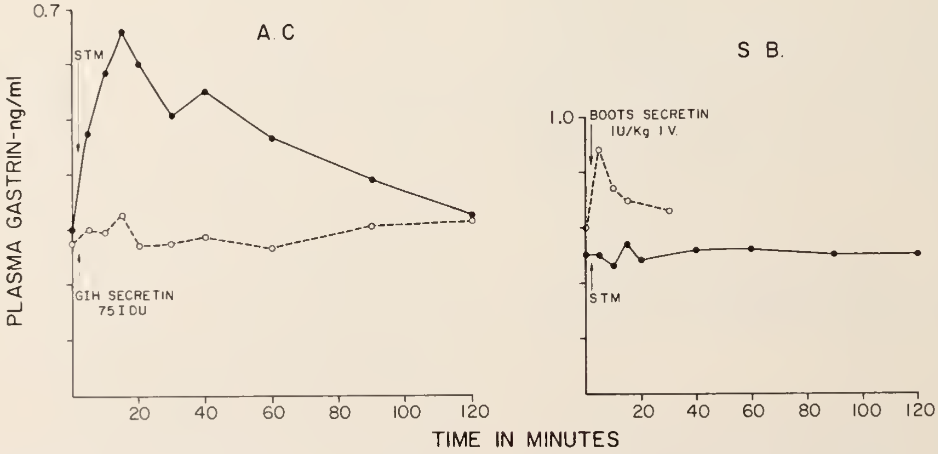

FIG. 1. Plasma gastrin before and after standard test meal (STM) (●——●) and before and after a secretin challenge (○– –○) in A.C., a patient with nontumorous hypergastrinemic hyperchlorhydria (NTHH), and in S.B., a patient with a proven gastrinoma.

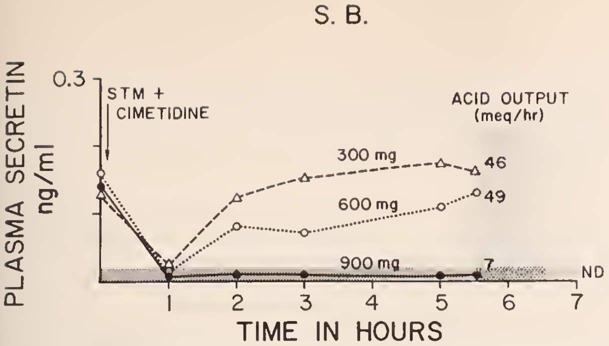

Fig. 3. Plasma secretin in patient SB before and after joint administration of a STM together with 3 dose levels of cimetidine. Acid output was measured at the end of each test.

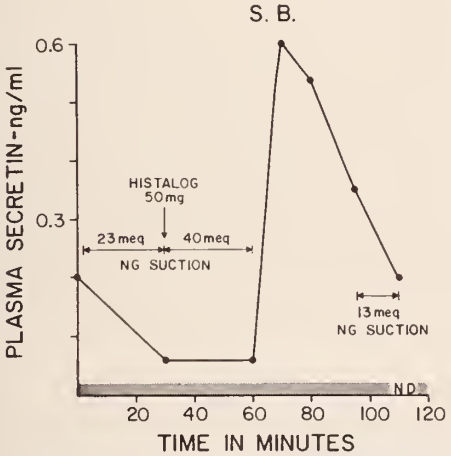

Fig. 4. Plasma secretin before and during a Histalog test. During asogastric suction (NG) plasma secretin fell rapidly due to removal of cid. Plasma secretin rose promptly when NG was interrupted.

he elevated basal levels (46–49 mEq/hr). Gastric acidity, ix hours after 900 mg cimetidine, was still reduced to even mEq/hr, consistent with the observation at 5 ½ ours that plasma secretin had remained undetectable.

Plasma secretin concentrations and acid secretory ates were determined at various times during the course f steady state and stimulated acid secretory testing (Fig.). Prior to beginning nasogastric suction the secretin evel was 200 pg/ml. During the first 30 minute collection, 3 mEq of acid were removed and secretin fell to 50 pg/ nl. During the 30 minutes following injection of Histalog, 0 mEq of acid were removed. When nasogastric suction vas interrupted, the secretin levels rose rapidly to 600 g/ml. Plasma secretin and acid secretory rates aproached basal values approximately one hour after Hisalog administration.

Discussion

The cases presented here typify the problems enconered in the diagnostic differentiation between patients ith a gastrinoma (ZE) and those with hypersecretion of gastrin from the G cells (NTHH). Both patients had marked basal hypergastrinemia and gastric acidity. Both failed to remain symptom free on the usual doses of cimetidine. The ZE patient, SB, showed a marked increase in acid release during a Histalog test (BAO 46 mEq/hr, MAO 80 mEq/hr). The presence of tumor in the head of his pancreas was of course an important diagnostic feature. However, the primary tumor is not often visualized in ZE. Provocative testing which exploits the differential gastrin release from mucosal G cells and gastrinomas is essential for diagnosis (5, 6). Patients with NTHH respond dramatically to a STM but fail to respond to a secretin challenge; responsiveness to these tests is exactly opposite for patients with ZE. The ZE patient fails to respond to a STM either because the tumor is not in the gastrointestinal tract or, if it is, it is not responsive to feeding. The normal G cells of the ZE patients are likely to be hyporesponsive to feeding because of the marked gastric acidity. Even if they were normally responsive, normal gastrin release is not likely to augment the already elevated basal levels. Secretin-stimulated gastrin release by the tumor appears to be dose-related (6). Another provocative test which has proven to be useful for diagnostic differentiation is a calcium challenge (2 mg Ca^{++}/kg intravenously) which stimulates gastrin release in the ZE patients but fails to provoke its release from normal G cells (6).

The increased diagnostic sensitivity and specificity made possible by gastrin RIA coupled with provocative testing that identifies the tissue source of circulating gastrin now permits earlier detection of ZE and can account for an apparent increase in its incidence. The diagnosis is now frequently made in the absence of the dramatic clinical manifestations once considered typical of the disease. Since we are a referral center, the cases of hypergastrinemic hyperchlorhydria coming to our attention may be atypical. However in our experience NTHH and ZE appear with approximately equal frequency. With earlier detection of ZE, there is now considerable overlap in basal gastrin in the tumorous and nontumorous states so that the differential diagnosis can be established only on the basis of appropriate provocative testing.

It is, of course, essential to demonstrate that hypergastrinemia is associated with hyperacidity. Hypoacidity, per se, promotes hypergastrinemia (1). Elevated gastrin levels, hypoacidity, and a gastric ulcer are more consistent with a diagnosis of gastric carcinoma than with a gastrinoma.

Measurements of gastric acidity should be an essential feature of the work-up of patients with symptoms of ulcer disease or watery diarrhea syndrome. Nonetheless, these studies are frequently performed poorly or not at all. In particular, with an increase in the use of H_2-receptor antagonists for the treatment of acid-peptic disease, an objective measure of acid responsiveness to therapy is required. To what extent can the simple measurement of plasma secretin replace the more cumbersome acid secretory tests?

Duodenal acidification is commonly accepted as a secretin secretogogue. Several laboratories have demonstrated that oral ingestion of acid in man and dogs promotes secretin release (8, 9). We have previously reported that basal endogenous hyperacidity is associated with basal hypersecretinemia and that there is a linear relation between plasma secretin and acid-secretory rate (7, 10). Gastric acidity in patient AC was not measurable due to continuous contamination of his gastric juice with bile. Nonetheless, it is evident from the studies described that in this patient changes in plasma secretin reflected changes in gastric acidity. In patient SB, direct comparisons could be made between plasma secretin and gastric acidity. Thus, an increase in gastric acidity during a Histalog test was reflected in a proportionate increase in plasma secretin; return of plasma secretin to basal levels following cimetidine reflected a return to basal hyperacidity; and plasma secretin was undetectable when the acid output was reduced to 7 mEq/hr. Thus, these studies confirm our earlier suggestion that measurement of plasma secretin is an expedient method for monitoring gastric acidity (10).

Cimetidine is now commonly employed in the management of patients with gastric hyperacidity (11). Generally a single dosage schedule, 300 mg four times a day, is employed. Monitoring the initial and continuing effects of this therapy has depended for the most part on assessment of symptom response or rate of ulcer healing. There have been reports of treatment failures but in most instances it is not possible to evaluate whether these failures were due to inadequate treatment or to the patients' becoming refractory to the blocking action of the drug. Objective monitoring by acid secretory studies is cumbersome and therefore is generally not employed; objective monitoring by measurement of plasma secretin is simple and can readily be used to determine the amount and frequency of administration of the drug required to reduce gastric acidity to the desired level. The usual therapeutic dose, 300 mg, did not assure in either of the patients described in this report adequate acid suppression during the ensuing 6-hour period. Therefore these patients would have been considered "treatment failures."

Feeding, anticholinergic and antacid therapy as well as cimetidine all promote reduction in gastric acidity. Drug therapy for many diseases is monitored not only by clinical responsiveness but also by objective measures of effectiveness. Adequate insulin therapy for diabetes is guided not only by how the patient feels but by measurement of blood or urine sugar; antithyroid therapy is now guided by measurement of circulating thyroid hormones. It is quite likely that as plasma secretin determinations become more readily available, they will find widespread application particularly in clinical problems characterized by marked hyperchlorhydria, such as ZE and NTHH. The optimal regimen of feeding, cimetidine, and other therapeutic agents can be established by monitoring plasma secretin to assure adequate reduction of gastric acidity.

The question as to whether true refractoriness to cimetidine therapy occurs cannot be answered at this time. In the cases which have been reported, it is generally not possible to determine whether the apparent refractoriness was due simply to inadequate dosage.

For many years the treatment of choice for ZE patients has been total gastrectomy in spite of the considerable operative mortality and well-known postoperative hardships. However provocative testing coupled with the measurement of plasma gastrin can result in much earlier identification of the presence of a gastrinoma than was hitherto possible, perhaps even before the tumor has metastasized. Furthermore, with H_2-receptor blocking drugs, long term palliation of symptomatology associated with hyperchlorhydria appears now to be possible. Considering the new modalities for diagnosis and therapy, the question can be raised again as to the circumstances under which a curative resection of the primary tumor should be attempted since, if this is not successful, the patient will eventually succumb to metastatic disease.

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A Multidisciplinary Approach to Alcoholism

CHARLES S. LIEBER, M.D., LAURE BRANCHEY, M.D., AND THERESA WORNER, M.D.

Introduction

It is now generally recognized that alcoholism is a major social problem confronting our society. Particularly disquieting has been its steady growth. Indeed, there has been a tremendous increase of alcoholism in this country over the last three to four decades. At present, it is estimated that there are ten million alcoholics in the United States. In a large system of hospitals, such as that of the Veterans Administration, alcoholism and its medical complications are considered second only to cardiovascular disease in magnitude. According to the official statistics, 20% of all discharges had alcohol-related disorders and 42% of all mental disorders were recorded as alcohol-related. These are high figures indeed if one considers that the official statistics undoubtedly underrepresent the true situation since discharge coding for alcoholism encompasses only a segment of alcohol-related diseases. For example, medical complications such as pancreatitis or trauma sustained during gross intoxication frequently go unreported as alcohol-related. Recent spot checks on our general medical wards revealed an approximate 50% incidence of alcoholism in the current patient population.

Theories of the etiology of alcoholism are numerous and no single theory has proven adequate to explain this syndrome. Obviously alcoholism is a disease state with a variety of causes and a complex course. An approach to the treatment of this disorder should thus be multifaceted and should include biological as well as psychological therapeutic modalities. We describe herein a multidisciplinary approach that is being implemented at the Bronx Veterans Administration Medical Center.

Rationale for a Biological Approach

A biological approach is indicated in view of the impact on our society of some of the medical complications of alcoholism (1). For instance, incidence of cirrhosis of the liver has now reached such proportions that it has become, by itself, a major public health problem. We now recognize that 75 percent of all deaths attributable to alcoholism are due to cirrhosis of the liver. Nationwide, cirrhosis has overtaken diabetes as the fifth largest cause of mortality; in large urban states, it has become the third cause of all deaths in the active age group of 25 to 65 years old. Of course not all cirrhotic subjects are alcoholics. Sometimes liver scarring can result from other liver diseases; however, it is generally recognized that a majority of patients with cirrhosis in this country admit to excessive drinking. Nevertheless, until a decade or two ago, it was generally agreed that this complication was not the direct effect of alcohol but was caused by the nutritional deficiences so commonly associated with alcoholism.

This prevailing view was unfortunate. By not recognizing the direct toxicity of alcohol, we denied ourselves a possible approach to the problem of alcoholism, particularly as it relates to control of its many complications. This outlook is now changing. Several studies including those we conducted in volunteer subjects given alcohol under metabolic ward conditions, and in the baboon fed ethanol with an adequate diet, have shown that alcohol unquestionably has direct toxic actions on many tissues, particularly the liver (2–4). The conclusion reached was that alcohol itself is responsible for various medical complications even in the absence of dietary deficiencies. Part of the mechanism involved has also been clarified in these and in other studies (2). Fatty liver develops, in part, because ethanol replaces fat as the main liver fuel. Liver injury progresses because of the deleterious effects of intracellular protein accumulation, toxicity of acetaldehyde, microsomal activation of hepatoxins, alterations in redox state, and lymphocyte cytotoxicity. Thus, it is clear that we are dealing with a toxic agent that is widely used and, therefore, commonly abused, thereby causing much medical and social harm.

One of the successful approaches to the problem of many diseases with broad medical and social impact has been the early detection of the affected subjects. It appears that among the alcohol users there is a subpopulation of very heavy drinkers who are particularly at risk

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From the Alcoholism Research and Treatment Center, Bronx Veterans Administration Medical Center and Mount Sinai School of Medicine, Bronx, N.Y. 10468

Requests for reprints should be sent to: Charles S. Lieber, M.D., Alcoholism Research and Treatment Center, Bronx V.A. Hospital, 130 West Kingsbridge Rd., Bronx, N.Y. 10468.

for the development of alcoholism and its complications. One treatment goal should be the early detection of those people prior to their social and medical disintegration. This might be achieved through some chemical marker of heavy drinking. There is reasonable hope that ongoing studies might be successful in the near future in providing us with a tool for the early detection of heavy drinking (5).

Another useful tool in the treatment of alcoholism could be the early detection of its medical complications through the use of improved blood tests. For example, blood tests for the detection of alcoholic liver disease have been developed recently with increased sensitivity or enhanced accuracy which we found to be provided by glutamate dehydrogenase (6). It has been shown that the activity of serum glutamate dehydrogenase correlates much better with the degree of liver necrosis and inflammation than serum transaminases. Such tests are now incorporated in our routine work-up of heavy drinkers to detect those with significant liver complications.

Since alcoholism and its complications do not develop in all heavy drinkers it is reasonable to speculate that some factors of heredity or individual susceptibility might play an important role in its etiology. In an effort to prevent cirrhosis, one major task is to better define the susceptible population. We have approached this problem in our baboon model of alcohol liver injury. In only one of three baboons fed alcohol long-term does cirrhosis develop. We have now learned to recognize lesions in the liver at a very early precirrhotic stage, that enable us to predict which animals are prone to the rapid progression to the cirrhotic stage upon continuation of drinking. Indeed, in some baboons, perivenular sclerosis (fibrosis around the central veins) was observed as early as in the "simple" fatty liver stage, before more severe liver lesions developed. The degree of perivenular sclerosis correlated with an increase in portal blood pressure. Moreover, sequential biopsies performed over a six-year period showed that in all animals with perivenular sclerosis, fibrosis, cirrhosis, or both developed after continued alcohol consumption. By contrast, neither fibrosis nor cirrhosis developed in animals without perivenular sclerosis (7). Thus, in the experimental model, the presence of perivenular sclerosis makes it possible to predict the subsequent evolution towards cirrhosis at the fatty liver stage. Preliminary results in man also support the concept that the presence of perivenular sclerosis should be regarded as a warning sign that permits identification of patients in whom cirrhosis is likely to occur (8). In view of its obvious practical implications, we are now applying this finding to our patients.

Research Program

Obviously, further research is needed to enable us to better understand factors of individual susceptibility. We must also attempt to acquire a better understanding of the modes of action of ethanol on the body chemistry. It is reasonable to hope that a better understanding of these mechanisms might give us a handle with which to interfere effectively with the actions of ethanol. These various research approaches are currently being emphasized in our Alcohol Research Center. The activities of the Center and of our newly created Alcohol Dependence Treatment Program are closely interwoven. At present, this pertains particularly to the medical component of the program but we are actively attempting to expand our approach to the psychological and behavioral aspects.

Indeed acoholism is multifaceted and it is apparent that sociological, cultural, and psychological factors should also be considered in any model of causation and treatment. The policies of early detection of excessive alcohol consumption outlined above should be applied to the social and psychological approaches as well. Recent studies have shown that the use of alcohol is increasing among young people and that it starts at earlier ages. Nearly 40 percent of junior and senior high school students drink alcoholic beverages. A recent survey has shown that 8% of a population of fourth, fifth, and sixth graders in the western United States drink at least once a week. These figures highlight the need for early intervention. An alcoholic patient with a long drinking history who has developed a chronic brain syndrome, and whose memory, comprehension, and judgement have been impaired, is less likely to respond to treatment as well as a patient whose experience with alcohol has not been as prolonged. Both patients must be helped but it can be hoped that early intervention will alter the course of the illness and prevent a young patient from developing into a chronic alcoholic.

Of course not every alcohol abuser will become an alcoholic. A better definition of the susceptible population could play a role in our strategy against alcoholism. This could be accomplished through longitudinal prospective studies investigating a variety of sociocultural and psychological factors in target populations.

Over the past few years, a large amount of public funds has been invested in treatment programs for alcoholics. A great variety of services are offered including detoxification, rehabilitation, residential and outpatient treatment programs, as well as psychological or psychiatric treatment modalities. Different assumptions about the causes of alcoholism underlie most of these treatment approaches. To date, no consensus has been reached about the etiology of alcoholism or about its most effective remedies. Evidence for the effectiveness of therapeutic modalities based on psychological models is still marginal. One of the priorities for professionals involved in the delivery of care to alcoholic patients should thus be the evaluation of the efficacy of all treatment modalities presently in use. One could compare the overall effectiveness of inpatient care to that of outpatient care, or examine the effectiveness of treatment for groups of patients representing different levels of impairment and different social backgrounds. Attempts could also be made to compare the recovery of patients entering treatment with those who make contact with a treatment facility but do not get involved in treatment. Some of these evaluations will hopefully be accomplished by our newly created Alcohol Dependence Treatment Program.

Structure of the Alcohol Dependence Treatment Program

The Alcohol Dependence Treatment Program of the Bronx VA Medical Center is unique in that it combines and integrates services offered by the Departments of Medicine, Psychiatry and Psychology. Some of the components of the program are:

1) Alcohol detoxification
2) Inpatient identification and treatment of medical complications of alcoholism
3) Inpatient rehabilitation from alcohol
4) Outpatient (combined medical and psychiatric) treatment

Alcohol detoxification

Patients in need of alcohol detoxification or those who show signs of alcohol withdrawal are admitted to a desgnated bed on the medical service. Patients with an ncomplicated detoxification have an average hospital stay of five to seven days. Following detoxification the patient is transferred to the inpatient rehabilitation unit f he is a suitable candidate (vide infra). Patients not wishing further inpatient therapy are discharged to the outpatient clinic. Patients with a medical or psychiatric omplication are treated on the appropriate ward following detoxification.

Medical complications

Patients with medical complications of alcoholism are reated on a medical ward, where the importance of the nderlying alcohol etiology is emphasized. In addition, ttention is focused on defining early lesions in patients with chronic medical complications of alcoholism.

npatient rehabilitation unit

This unit is designed to enhance the process of recovry started on the detoxification unit. Care is provided y a multidisciplinary staff headed by a psychiatrist. The verage length of stay on the unit is four to five weeks. prolonged stay in a hospital setting allows patients to ecome aware of the seriousness of their illness and to ngage in a variety of treatment modalities. Treatment ncludes individual, group and behavioral psychotherapy, orientation to educational and vocational rehabilitation, alcohol education seminars, and occupational therapy.

The rehabilitation unit offers patients a unique opportunity for the treatment of medical conditions that necessitate care beyond the detoxification period. Before patients leave the unit, efforts are made to engage them in planning for continued care in the clinic after completion of this phase of treatment.

Outpatient unit

Medical component–Patients with medical complications of alcoholism are treated with currently accepted therapeutic regimens. Emphasis is placed on both detection of alcoholism and detection of relapse through the use of recently described biochemical markers. Screening of patients for severe medical complications is available through the routine use of newly described laboratory tests, such as glutamic acid dehydrogenase.

Rehabilitation component–The long-term psychological treatment of alcoholic patients is carried out in the rehabilitation component of the outpatient unit. Patients are offered an individualized and comprehensive treatment program. The importance of sobriety is stressed although this is not the sole objective of the program. Many of our patients suffer from some underlying emotional problem. Some patients have recognizable psychiatric illnesses ranging from adjustment reaction to schizophrenia. Others drink to relieve anxiety, depression, feelings of inadequacy and of loneliness. Patients who become sober can still experience the problems that caused their alcoholism. For this reason our staff attempts to treat the psychiatric or psychological problems of each patient. The treatment modalities used include counseling, individual, and group therapy.

In order not to encourage the replacement of one addiction by another, we stress a drug-free approach. Tranquilizers are used only if it is felt that anxiety precipitates relapses and cannot be dealt with in other ways. Antabuse is offered to all motivated patients, but its use is not compulsory.

Attempts are made to provide patients with alcohol free environments. The clinic runs a day lounge offering a variety of activities. Attempts are also made to provide patients with an environment outside the clinic where the temptation to drink will be lessened. This can be accomplished, for example, by offering some patients a place of residence or by helping them move away from their drinking companions. We encourage our patients to utilize community resources. Whenever indicated, we help establish interested patients into AA groups. When a patient has recovered sufficiently, he is directed to the vocational rehabilitation resource person.

In essence the new Alcoholism Program at the Bronx

Veterans Administration Medical Center results from an amalgamation of three components: the Alcohol Research Center, a Medical Treatment Program and a Psychiatric Treatment Program. Although in each component many aspects are traditional, it is hoped that especially favorable results will be derived from the interdisciplinary integration. Experimental findings raise the hope for improved early detection of either heavy drinking, liver disease or predisposition to cirrhosis. These approaches are being verified in a clinical setting as soon as practical. Application of experimental results to the clinical condition is essential as the ultimate test of its usefulness and relevance. When the experimental data and clinical application take place in different units or institutions, the transfer process is usually slow and may sometimes take decades. One of the goals of our center is to accelerate this process of transfer of laboratory data to patient management. Another purpose is to apply sound research principles to all aspects of diagnosis and treatment of the alcoholic, including psychiatric, psychological as well as medical treatment modalities.

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Latent Left Ventricular Dysfunction and Response to Exercise in Patients with Chronic Alcoholism

PAUL SCHWEITZER, M.D. AND HERBERT MARK, M.D.

Abstract

The response to maximal exercise was studied in thirty patients with chronic alcoholism and twenty healthy subjects who served as control models. Left ventricular function was evaluated by measuring the systolic time intervals. Alcoholic patients demonstrated a prolonged preejection period and an increased preejection period (PEP)/left ventricular ejection time (LVET) ratio. The duration of exercise and the performed work were similar in the control group and in the alcoholic group. The achieved maximal heart rate was lower and the increment of the systolic blood pressure during exercise was less in alcoholics than in the control patients. The possible mechanism underlying these hemodynamic changes is discussed.

Introduction

Recent studies of the effects of alcohol on the heart rate have demonstrated functional impairment even in the absence of overt clinical heart disease. In studying the hemodynamic effects of chronic alcoholism on exercise, Slany et al showed that patients with chronic alcoholism are able to perform the same maximal exercise as healthy subjects despite an abnormal increase in pulmonary artery diastolic pressure (1). A more pronounced increase of left ventricular end-diastolic pressure in a group of alcoholic patients in comparison with normal controls was demonstrated by Gould and his coworkers when studying the response to a single workload (2). These exercise-induced hemodynamic abnormalities support the observation of various physicians that alcoholic patients appear to have latent left ventricular malfunction (3–8). Regan et al demonstrated impaired left ventricular function during angiotension infusion in patients with longstanding alcoholism, while Spodick et al, and Wu et al, measuring systolic time intervals by noninvasive methods, showed a prolongation of the preejection phase of left ventricular contraction as additional evidence of left ventricular malfunction in alcoholics (3, 6, 7).

An abnormal increase in end diastolic pressures or a prolongation of the preejection phase of left ventricular contraction do not necessarily mean that ventricular contractility is decreased because they may result from decreased compliance of the left ventricle (7). Furthermore, the contractile state is only one of the many factors that may influence total cardiac function, particularly cardiac output (9). In alcoholic patients, therefore, exercise performance may remain normal despite abnormalities in myocardial mechanics. To confirm this hypothesis, we analyzed by noninvasive means the response to maximal exercise in patients with chronic alcoholism.

Materials and Methods

We studied the response to exercise of twenty normal controls (group I) and thirty male patients with a history of chronic alcoholism (group II). The control group consisted of members of the medical house staff and medical students. The history, physical findings, and the electrocardiogram (ECG) were normal in all of these subjects. Group II included patients who had been drinking heavily for at least five years, and whose liver biopsy showed either alcoholic hepatitis or fatty liver. Patients with cirrhosis were excluded from the study. All patients in group II had normal cardiovascular findings, on the basis of clinical examination, ECG and chest x-ray. To minimize the likelihood that latent coronary artery disease was present, we included only patients less than forty years of age. Coronary arteriography was not performed. In addition, no patient in group II had a positive stress test. All patients with chronic alcoholism were studied after a diagnosis of alcoholic liver was confirmed histologically and all underwent exercise testing at least seven days after admission and discontinuance of drinking.

From the Department of Medicine, Bronx Veterans Administration Medical Center, Bronx, N.Y. 10468.

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The maximal exercise test was performed on a bicycle ergometer using an initial workload of 300 kilometers per minute (KPM), which was increased by 150 KPM every three minutes without interruption. Exercise was stopped if the patient developed chest pain, significant arrhythmias, marked shortness of breath, or fatigue. Six limb leads and precordial lead V5 were recorded in the supine and sitting positions before exercise, immediately after exercise, and three, five and eight minutes later. During exercise, lead V5 was monitored and recorded at the end of every minute. In addition, the ECG was monitored for arrhythmias ten minutes after exercise. Blood pressure was measured by auscultation in a sitting position before, during, and at the end of exercise.

In fifteen subjects in group I and in twenty-six patients in group II, the left ventricular performance was evaluated by analysis of the systolic time intervals according to the method of Weissler et al (10). The systolic time intervals were measured from ECG lead II, heart sounds and carotid pulse tracings that were simultaneously recorded on photographic paper using a paper speed of 100 mm/second. The QS2 interval recorded in this manner permits measurement of electromechanical systole. The interval between the onset of the carotid pulse upstroke and closure of the aortic valve (S2) reflects left ventricular ejection (LVET) and that from the Q wave to the start of the carotid pulse, the preejection period (PEP). At each phase of the study, systolic time intervals were measured from an average of ten cardiac cycles. The systolic time intervals were corrected for the heart rate (PEPI and LVETI).

Results

The systolic time intervals of both alcoholic and control patients are seen in Table I. A statistically significant prolongation of the PEPI and an increase of the ratio of PEP/LVET are demonstrated in patients with chronic alcoholism. On the other hand, the LVETI was similar in both groups, and the QS2 was only insignificantly longer in alcoholics than in normals. These results suggest the presence of a subclinical left ventricular malfunction in the patients of group II.

Table II shows the response to maximal exercise in both groups. The mean age in both groups of patients was similar. The resting heart rate was 79/min in group I and 86/min in group II; this difference was not significant ($p > 0.05$). In the control group, the maximum heart rate achieved was 174/min and in alcoholics 149/min. The difference between these two groups is significant. ($P < 0.01$) The resting systolic blood pressure was lower in group I (114 mm Hg) than in group II whose systolic blood pressure before exercise was 136 mm Hg, a statistically significant difference ($p < 0.01$). Exercise increased the systolic blood pressure in the control group to 153 mm Hg in group I and to 157 mm Hg in group II. The difference between the systolic blood pressures during exercise was no longer significant ($p > 0.05$). In other words, in normal subjects the increment during exercise was 33 mm Hg but, in alcoholics, only 21 mm Hg. The resting diastolic blood pressure was 73 mm Hg in group I and 78.8 in alcoholics. During exercise the diastolic blood pressure decreased in group I to 62.7 mm Hg and to 71 mm Hg in group II. The differences in diastolic pressures before and during exercise between these two groups of patients were not significant ($p > 0.05$). The duration of exercise was 553 seconds in group I, and 516 seconds in group II. The difference is not significant ($p > 0.05$).

Discussion

Our findings are in agreement with the results of Wu et al, who found that alcoholics have a prolonged PEPI, and increase of the ratio of PEP/LVET, and normal LVET (7). On the other hand, the alcoholics studied by Spodick et al demonstrated a prolongation of the PEP but also a shorter LVET (6). The discrepancy between our findings and those of Spodick may have been caused by a difference in patient population. We studied alcoholics who were 14.4 years younger than Spodick's patients. It is possible that our group of alcoholics represented an earlier stage of alcohol-induced heart disease, with prolongation of the PEP but no change in the LVET.

Another difference between the alcoholics and normal subjects was the resting systolic blood pressure. Patients with chronic alcoholism had a significantly higher systolic blood pressure at rest in the sitting position than

TABLE 1
Systolic Time Intervals in Patients with Chronic Alcoholism

Group	Age yr	Heart rate min	PEPI* msec	LVETI** msec	QS_2 msec	$\frac{PEP}{LVET}$
Control (15)	29.4	70 ± 12.29	121 ± 14.63	403 ± 19.90	525 ± 29.40	0.32 ± 0.04
Alcoholic (26)	30.6	77 ± 14.30	140 ± 14.38	402 ± 27.88	537 ± 22.33	0.41 ± 0.08
p value	>0.05	>0.05	<0.01	>0.05	>0.05	<0.01

* Preejection Period Index.

** Left Ventricular Ejection Time Index.

TABLE II
The Effect of Exercise on the Heart Rate, Blood Pressure and Duration of Exercise

Group	Age	Heart rate		Blood pressure				Duration of exercise
	yr	min		mm Hg				second
		R	E	Systolic		Diastolic		
				R	E	R	E	
Control (20)	29.5	79 ±24.8	174 ±10.83	114 ±32.15	153 ±20.11	73.0 ±8.94	62.7 ±13.12	553 ±96.04
Alcoholic (30)	31.7	86 ±10.62	149 ±18.64	136 ±38.57	157 ±34.82	78.8 ±38.4	71.0 ±25.25	516 ±125.47
p value	>0.05	>0.05	<0.01	<0.01	>0.05	>0.05	>0.05	>0.05

normals. This observation is consistent with a recent report by Klatsky et al suggesting that prolonged and excessive intake of alcohol may be a risk factor for the development of hypertension (11). Because the number of patients studied was small and the absolute value of the systolic blood pressure was not in the hypertensive range, the relationship between alcoholism and hypertension needs further study.

Our results also demonstrate that patients with alcoholism are able to perform the same exercise as normals, despite abnormalities in myocardial mechanics. This observation is not completely unexpected. A decrease in the contractile state or an increase in stiffness of the left ventricle does not necessarily mean that the pumping function of the heart is impaired. A similar discrepancy between the effect of alcohol on the systolic time intervals and the effect on exercise was demonstrated in normal subjects. Gould and others showed that acute ingestion of alcohol by healthy individuals prolongs the PEP and increases the PEP/LVET ratio (12, 13). On the other hand, alcohol intake has no effect on exercise performance in normal subjects (14, 15).

It should be pointed out, however, that despite similar exercise performance, the response to exercise was not the same in both groups. The most important difference was that in alcoholics the maximal heart rate achieved and the increment of the systolic blood pressure during exercise were less than in normals. The causes of inadequate heart rate response and systolic blood pressure response to exercise in alcoholics are not known. According to Bruce et al, lower maximal heart rate and systolic blood pressure, associated with shorter duration of exercise, suggest left ventricular impairment (16). While the duration of exercise in patients with alcoholism was not significantly different from that of the normal control group, early left ventricular malfunction as the sole cause of inadequate heart rate and systolic blood pressure response has not been ruled out.

The combination of a lesser rise in heart rate and normal exercise performance indicates that, in early stages, alcoholics are able to achieve a cardiac output similar to nonalcoholic subjects and that the lower maximal heart rate is compensated for by an increased stroke volume. The smaller rise of systolic blood pressure also suggests that afterload during exercise was less in alcoholics than in the control group. An attenuated afterload may facilitate a higher stroke volume during exercise in patients with alcoholism. Other compensatory mechanisms, such as widening of the A-V oxygen difference or a smaller increase of muscle blood flow, could be alternative mechanisms underlying the observed hemodynamic changes in these patients.

Because we did not measure the cardiac output or other hemodynamic indices, we cannot define the mechanisms operating in patients with alcoholism during exercise. Further studies are needed to clarify the circulatory changes which occur in patients with alcoholism during exercise.

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General Surgical Evaluation of a Powered Device Operating at Ultrasonic Frequencies*

W. JOHN B. HODGSON, M.D., SANJIVANI BAKARE, M.D., ELIZABETH HARRINGTON, M.D., JERRY FINKELSTEIN, M.D., P. K. PODDAR, M.D., LOUIS L. LOSCALZO, D.D.S., JEAN WEITZ, M.D., AND A. JAMES McELHINNEY, M.D.

Introduction

The Cavitron Ultrasonic Surgical Aspirator™ (CUSA™) System has been evaluated in the surgical research laboratories at the Bronx Veterans Administration Medical Center. Following documentation of the results, it was used surgically and has helped several patients. The device consists of a power module and control console to which a handpiece is connected by means of tubing. The handpiece is the size of a large pencil and its powered titanium tip vibrates at ultrasonic frequencies so that tissue within a one to two millimeter radius of the tip may be fragmented and aspirated. It imparted tactile feedback to the surgeon who was able to develop three basic operative techniques. These were tissue dissection, particularly of blood vessels, tissue incision, and tissue aspiration.

Materials and Methods

Celiotomy was performed on five mongrel dogs, averaging fifteen kilograms in weight each, and the pancreas was identified. The CUSA™ System was used to remove a segment of pancreatic acinar tissue from a four to five centimeter length of pancreatic duct that, like proximal and distal pancreas, was left intact. Serum amylase levels were recorded immediately postoperatively and again four hours postoperatively. In one dog, the serum amylase level four hours postoperatively went up to 2,880 mg%, but no abnormal rises were noted in any of the other dogs. Five days postoperatively, the dog with the raised serum amylase developed peritonitis and wound dehiscence secondary to its acute pancreatitis and died. The remaining four dogs were reexamined in six weeks and in all cases the duct had apparently thickened and shortened so that the distance between the remaining distal pancreas and the proximal pancreas, that had been denuded of acinar tissue, had shrunk to about two centimeters.

Following these experiments, a 67-year-old black male was admitted with a history of two months of anorexia, weight loss and jaundice with a total bilirubin of 19.8 mg/ml. His preoperative workup indicated that he probably had a carcinoma of the head of the pancreas. This was suggested by the dilatation of the biliary system, shown on transhepatic cholangiogram, and by an abnormal head of the pancreas, shown on abdominal sonograms. At operation the diagnosis was confirmed. Local lymph nodes revealed only inflammatory reaction. It was decided to carry out a Whipple procedure in the normal manner except that transection of the pancreas at the portal vein would be done with the CUSA™ System. This very readily dissected out and illustrated the multiple small side branches of the portal and superior mesenteric veins that run into the body of the pancreas. Consequently, total control was available at all times and very little bleeding occurred (Fig. 1). A routine frozen section, taken from the resected neck of the pancreas, showed there was a small focus of tumor present. It was therefore decided to proceed to total pancreatectomy. This was again done with the CUSA™ System which dissected the pancreas off the splenic vein and artery with remarkable ease. Indeed, the spleen could have been retained with this dissection had not the case been one of carcinoma of the pancreas. It bears repeating that use of the CUSA™ System gave full visability and total control at all times during this operative procedure. Blood loss throughout was reduced to about two units. However, the anesthesiologist transfused three units of

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From the Department of Surgery, Bronx Veterans Administration Medical Center, Bronx, N.Y. and Mount Sinai School of Medicine, New York, N.Y.

Requests for reprints should be sent to: Dr. W. J. B. Hodgson, 1212 Fifth Ave., New York, N.Y. 10029.

* Based on a lecture entitled "Reduction in Blood Loss in General Surgery Using an Ultrasonic Device" given by Dr. Hodgson at surgical grand rounds on September 6, 1978 at The Mount Sinai Hospital.

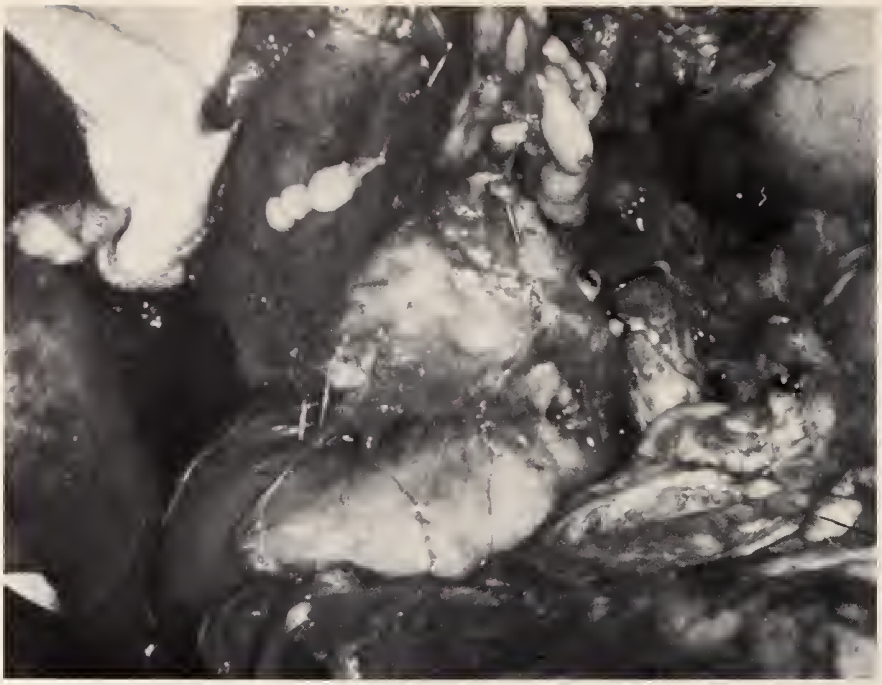

FIG. 1. Photograph of superior mesenteric and portal veins after dissection of neck of the pancreas entirely with the CUSA™ System.

packed cells and one unit of whole blood during the procedure. The patient tolerated the operation well and was sent to the surgical intensive care unit which he left in fine condition after four days.

Liver experiments have also been carried out and have in part been reported elsewhere (1, 2). Briefly, liver biopsies were performed in five dogs. In the first dog, catgut sutures were placed in the usual manner and liver biopsies were taken with the CUSA™ System and with a knife for comparison. It was noted that the biopsies taken with the CUSA™ System did not appear to bleed and that the liver architecture could easily be demonstrated. Thenceforth, the CUSA™ System was used to take liver biopsies without catgut control (Fig. 2). In all cases the liver architecture again was demonstrated easily; smaller vessels were cauterized directly with the tip of the CUSA™ System; larger vessels were demonstrated and clamped before being tied and cut. Next, a large three centimeter liver biopsy was taken bloodlessly from a baboon using the technique devised in the first few dogs. Subsequently, left hemihepatectomies were performed in five additional dogs. Two of the dogs were used as controls and a standard technique was used. The other three dogs had experimental left hemihepatectomies carried out using the CUSA™ System. Here, a direct approach was used starting anteriorly, and gradually deepening the incision through the liver capsule downwards, with exposure of the vessels and with the biliary tree in a sequential fashion, both toward the portahepatis and toward the inferior vena cava, until the procedure was completed. Then the caudate lobe was also removed using the CUSA™ System. In both control and experimental groups an average of twelve grams of liver per kilogram of body weight of dog was resected. The procedure was completed in about half the time using the CUSA™ System compared with conventional techniques. Hemoglobin, hematocrit, liver function and electrolyte balance was charted pre and postoperatively. There was no statistical difference in results in the two groups. All dogs survived postoperatively without any significant change in blood tests.

A 62-year-old Caucasian male had developed a metastatic tumor in the left lobe of his liver following a resection of a Dukes' C carcinoma of the sigmoid colon, fourteen months earlier. His initial carcino embryonic antigen was less than 0.5 nanograms/ml but had risen to 7.6 nanograms/ml. He had a postoperative liver scan with a peripheral defect in the left lobe of the liver. His angiogram showed encasement of the left hepatic artery proximal to this defect. At laparotomy he had two metastatic nodules in the left lobe of the liver, the largest of which was four centimeters in diameter. He also had a small two centimeter nodule on the dome of the right lobe of the liver. It was decided to debulk his metastatic tumor with a wedge resection of the left lobe of the liver using the CUSA™ System. Glisson's capsule was incised with a knife about two centimeters medial to the tumor masses. The CUSA™ System was employed to deepen the incision and to cauterize smaller vessels. Larger vessels were dealt with using clips or ties. As the dissection continued the left branch of the portal vein was cleared laterally and all its branches were visible on this side so

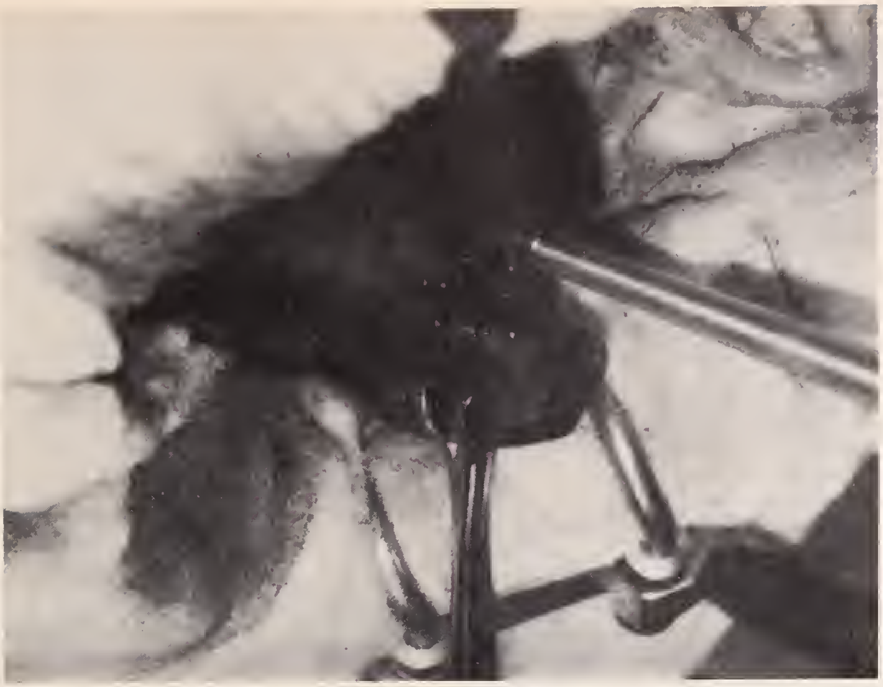

FIG. 2. Liver biopsy in the dog with the CUSA™ System.

that they could be clamped, tied and divided. Again, full control was available throughout the entire procedure and there was never any need for hemostatic through and through catgut sutures to be applied; and as in the dogs at the end of the procedure, the cut surface of the liver was dry. In the dogs, no drains had been used and on reexamination six weeks postoperatively there had never been any evidence of hematoma. Nonetheless, it was decided to place two large closed drains in the left upper quadrant and although 25% of the liver was resected, only two units of blood were required throughout the entire procedure. Postoperative recovery was totally uneventful.

Results

Five, fifteen-kilogram mongrel dogs had partial splenectomy performed using the CUSA™ System. No attempt was made at applying hemostatic sutures before transection of the spleen. It was beneficial to incise the capsule of the spleen first with a knife and then to deepen the incision with the CUSA™ System. Occasional vessels were encountered and these were tied. Otherwise, transection of the spleen was uneventful. No postoperative bleeding occurred in any dog, including one which has been kept for two months postoperatively. It is possible in view of the renewed interest in partial splenectomy that it may be an opportune time to consider the use of the CUSA™ System in partial splenectomy in patients (3). However, we do not as yet have clinical experience at this hospital with partial splenectomy.

When the CUSA™ System was used on the dog kidney there was no hemostatic effect and therefore further experiments were abandoned (1).

Three, fifteen-kilogram mongrel dogs had partial pneumonectomy performed using the CUSA™ System. Considerable difficulty was encountered in trying to get through the visceral pleura and this was solved by carefully incising the pleura with a sharp scalpel first. Thereupon the CUSA™ System was used to literally cut through the lung substance and to apparently seal the surface. This was tested by filling the chest cavity with saline which appeared to confirm this.

Two nonsurvival experiments were carried out in dogs (2). The first had partial glossectomy performed entirely with the CUSA™ System and bleeding was minimal. Following this a hemiglossectomy was carried out in a dog again with minimal bleeding. Since the tongue is an exceedingly vascular organ and much bleeding and blood loss occurs in surgery of the tongue it was decided to move rapidly into this clinical arena. Eight patients with cancer of the tongue have been operated on and considerable reduction in blood loss has occurred in every case using the CUSA™ System. We are particularly pleased with our progress in accurate identification of blood vessels (Fig. 3). We have found that bleeding from the normally highly vascular and difficult pterygoid plexuses has been almost eliminated with the CUSA™ System. Our technique when operating on the tongue has been to place marking sutures to delineate tumor free area and then to incise the tongue capsule with the Bovie and then to deepen this incision with the CUSA™ System,

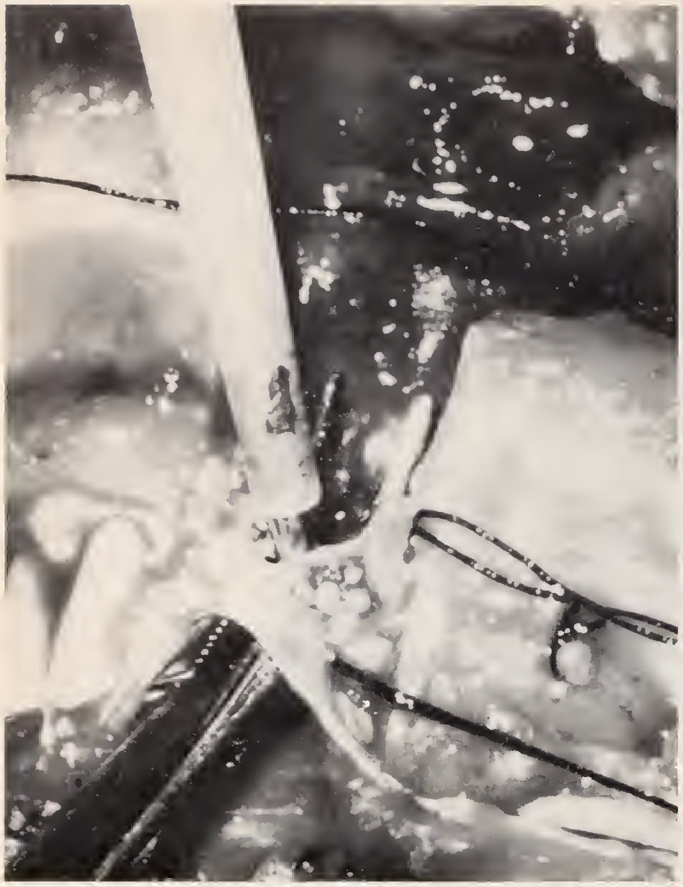

FIG. 3. Demonstration of the lingual artery and its branches in the tongue during resection with the CUSA™ System.

using it to divide muscle and dissect vessels that were then secured. We have had no postoperative problems and no sloughing of the tongue remnant even though up to three quarters of the tongue may have been taken using this technique–perhaps because the technique is so clean and there is no charring.

In experiments on the hollow viscera of the dog, the CUSA™ System was used to incise the stomach and bowel walls (1). The procedure was achieved, but it was slow. However, hemostatic effect was admittedly greater than an incision made with a knife. Effects of mucosectomy in the gastric corpus, antrum and small bowel were studied. It was found that the loose mucosa of the gastric corpus was more easily dissected using scissors than using the CUSA™ System. However, when the mucosa was tightly applied as in the antrum and in the bowel, it was possible to directly strip mucosa from submucosa by fragmentation and aspiration with the CUSA™ System. In the bowel, if a one centimeter strip of mucosa was excised in this manner, within a week it had regenerated. However in the stomach, regeneration of mucosa was only partial within one week. Attempts to dissect out a cylinder of mucosa from the wall usually resulted in defining a plane outside of the submucosa and inside the muscle. This usually resulted in a perforation of the bowel wall and it was decided that in the dog this approach was unsatisfactory. Experiments in stripping mucosa are continuing in the dog.

Discussion

The so called acoustic vibrators have been on the scene for nearly ten years (4). Kelman has performed over 500 cataract emulsifications over a five-year period with the Phaco-Emulsifier which was the precursor of the CUSA™ System(5). He has had some problems that occur in cataract surgery such as striate keratitis, opacification of the posterior capsule, vitreous adhesion to the wound and retinal detachment. These complications, however, are of the same order using traditional techniques.

Attempts have been made to use the Phaco-Emulsifier on tissue other than cataracts but without success. The CUSA™ System is the logical outgrowth. The instrument has a powered tip, vibration being produced by a magnetostrictive device that employs the principle of resonant vibration of a long slender metal structure maintained by an alternating electric current of the exactly required frequency. The frequency is 23 KiloHertz and produces a maximum stroke at the vibrating tip of 300 microns that, if charted, would describe a sine wave. The excursion is not uniform and very high velocities can be obtained at the extremity. The powered instrument is cooled as it produces a great deal of heat; also irrigating saline is regulated at the tip so that some of this heat may be used in cauterization of smaller vessels.

The first use of the CUSA™ System was in neurosurgery when Flamm et al tried the machine's effect on the exposed cat spinal cord (6). After continuous action for thirty minutes of the ultrasonic aspiration tip, placed two to three millimeters away with an intact dura, there was no permanent effect. When the same experiment was done with the dura opened, paraplegia occurred. Microscopically there were areas of hemorrhage, edema, and glial scarring in the animal spinal cords; but there is no comparable situation in clinical use where the tip would be fixed in one place, two to three millimeters away from any organ, and left in continuous operation for thirty minutes. Flamm et al went on to report thirty-eight excisions of neurologic tumors from the brain and spinal cord without any side effects. In particular, they were able to remove one meningioma situated between the optic nerve and carotid artery without damage to either structure (6).

In our unit, we were evaluating the CUSA™ System from scratch as there was no known information on its behavior in the general surgical situation. Therefore it was necessary to first carry out basic animal experiments. We have demonstrated that there are three modes of action of the CUSA™ System. These are tissue dissection, particularly of blood vessels, tissue incision, and tissue aspiration. Because of these modes of action we have been able to test out the CUSA™ System successfully on the pancreas, liver, spleen, lung and also in the G.I. tract. It has been used clinically in carcinoma of the pancreas, metastatic disease of the liver, and carcinoma of the tongue. Each case has given us more experience and as our experience has increased, we have gained more surgical control using the CUSA™ System. We are experimenting in different branches of surgery and we believe our present and continuing results in the use of the CUSA™ System are very encouraging.

Conclusions

Animal experiments and pilot studies in patients using a powered device operating at ultrasonic frequencies demonstrated that surgical procedures such as total pancreatectomy, partial hepatectomy, tongue resection, and "fulguration" of rectal cancers can be carried out safely and probably more efficiently using this powered device than using standard surgical techniques. Our experiments have demonstrated a consistent reduction in blood loss and a consistently good postoperative recovery without any evidence of tissue necrosis. We are continuing our general surgical evaluation of the powered device operating at ultrasonic frequencies both clinically and in our laboratories.

Acknowledgements

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Histologic Evaluation of Tissues Sectioned by Ultrasonically Powered Instruments (a Preliminary Report)

JOSEPH W. WILLIAMS, M.D. AND W. JOHN B. HODGSON, M.S., F.R.C.S.

A study of the use of ultrasonically powered instruments in the laboratory and clinical setting in general surgical procedures is under way at the Bronx Veterans Administration Medical Center and has been reported elsewhere (1). There have been reports on the use of ultrasonically powered instruments in cataract surgery, otolaryngology, and neurosurgery (2–5).

In this study, biopsies were taken from dogs using the Cavitron ultrasonic aspiration device and the surgical scalpel. During the operation, it was noted that there was considerably less bleeding associated with the use of the ultrasonic device than with the scalpel, most noticeable in vascular organs such as the liver and spleen. Biopsy specimens were examined in the histopathology laboratory without prior knowledge of which biopsies were taken with the scalpel and which were taken with the ultrasonic device—particular attention being paid to the cut edges and surfaces.

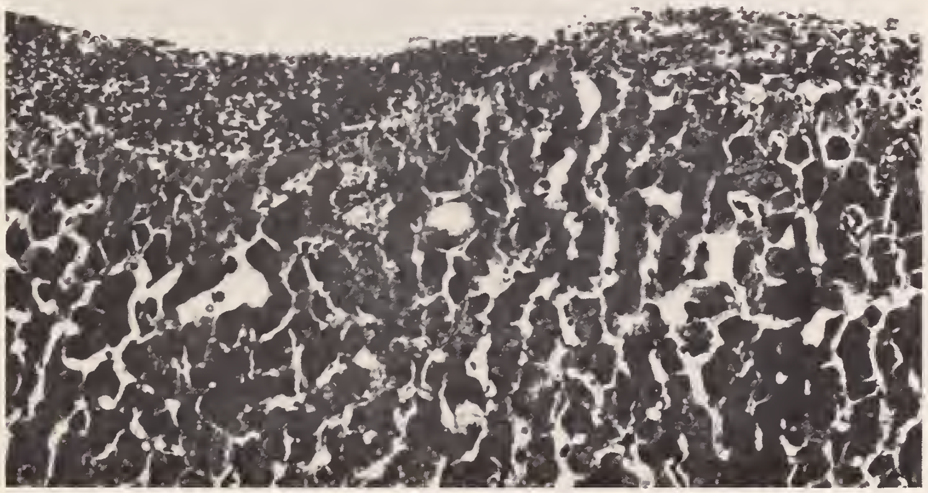

FIG. 1. Ultrasonically cut edge of liver showing closely adherent layer of erythrocytes with a layer of pale hepatocytes at the edge.

Macroscopically, in formalin-fixed specimens, some surfaces were seen to be smooth and regular. These were later found to have been made by the scalpel. In other specimens, the surfaces were rougher and covered by a dark coagulum. These were cut with the ultrasonic device.

On histologic examination of hematoxylin and eosin-stained sections, the tissues with a smooth surface had

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From the Departments of Pathology and Surgery, Bronx Veterans Administration Medical Center and Mount Sinai School of Medicine, N.Y.

Requests for reprints should be sent to: Joseph W. Williams, M.D., Bronx Veterans Administration Medical Center, 130 West Kingsbridge Road, Bronx N.Y. 10468.

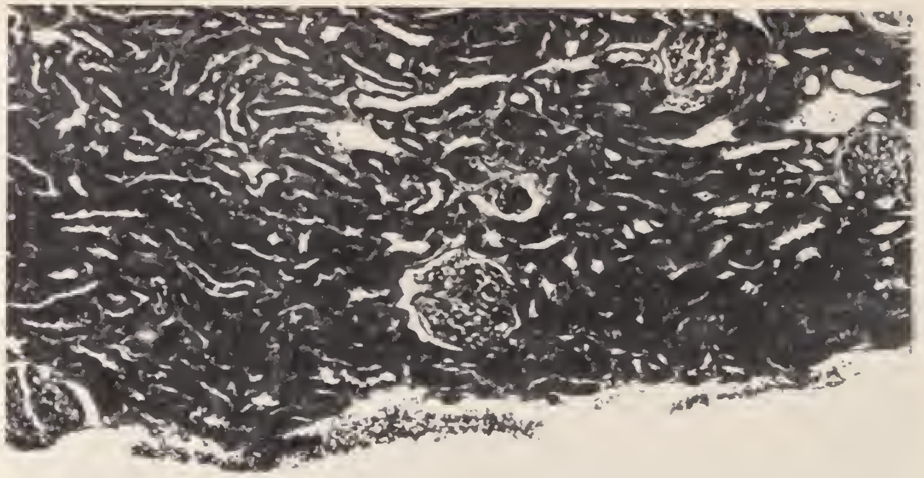

Fig. 2. Ultrasonically cut edge of kidney showing a loose layer of erythrocytes, discontinuous and separated from the renal cut edge.

clean cut edges with well-defined cells right up to the edge. Those with the rougher surfaces had irregular edges with a layer of erythrocytes adherent to the surface. A variable number of cells at the edge were pale and hazy and appeared as a pale line just beneath the edge. In later specimens this pale line was much less evident, but the layer of erythrocytes at the surface was still present (Fig. 1). Remarkably, these erythrocytes do not seem enmeshed in fibrin but can be individually distinguished where not overlapping. The thickness of the layer of erythrocytes varied from 2 to 20 or more red cells. The layer was closely adherent to the surface in the liver, spleen and lung, but discontinuous and separated by a distance of about 20 microns in the kidney (Fig. 2). At first this was thought to represent hemorrhage. However, it was later appreciated that there were some curious features about the layer of red cells. In spite of the absence of any fibrin it appeared "bonded" to the surface and not lost in processing. Also, the presence of the red blood cell layer correlated well with the hemostatic effect at operation; that is, where it was closely adherent to the surface there was little bleeding at operation. There appears to be a correlation between the "bonding" of red cells to the surface and the lack of hemorrhage at operation. When there was no close bonding, as in the kidney, there was pronounced hemorrhage at operation. The less than expected hemorrhage with the use of ultrasonic device had also been noted by others in otorhinolaryngologic procedures. The possibility that a "hotter" setting of the instrument may produce better hemostasis in the kidney is being investigated.

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Preliminary Feasibility Studies Using an Ultrasonic Device for Endarterectomy

JERRY L. FINKELSTEIN, M.D., W. JOHN B. HODGSON, M.D., A. JAMES McELHINNEY, M.D., AND ARTHUR H. AUFSES, JR., M.D.

Introduction

In the surgical research laboratories of the Bronx Veterans Administration Medical Center, we have been evaluating a powered system in general surgery (1, 2). This is the Cavitron ultrasonic surgical aspiration™ (CUSA)™ System and consists of a handpiece and free-standing control module. The titanium tip of the handpiece vibrates at ultrasonic frequencies and thus fragments and aspirates tissue. This action has been found to be selective and under the surgeon's control. A preliminary feasibility study using this device for endarterectomy was carried out.

Incentive for our study takes origin in the previous unimpressive clinical results for endarterectomy (3). The most frequent complication after endarterectomy is a recurrent stenosis from progressive fibrosis and narrowing of the arterial wall (4). There are also the immediate problems at the distal end of the endarterectomized vessel. The intima is usually abruptly cut off and has a tendency to dissect, or to narrow the lumen and cause thrombosis, or even to take part in embolization. If reconstruction is limited to the aorta and common iliac arteries, the five-year results are similar for endarterectomy and bypass grafts. Kouchoukos et al reported a series of 206 patients treated either by endarterectomy or bypass grafting after which the five-year patency rates were virtually identical 62% and 63% of the time (5). Szilagy reported similar results five years after operation with patency rates of 85% and 89%, respectively, when comparing endarterectomy and bypass grafting (6). The most frequent late complication after bypass procedures are false aneurysms developing at the suture line; not to mention, of course, the potential complications anytime foreign material is implanted into the body.

As far as femoropopliteal occlusive disease is concerned, the results are markedly poorer. Endarterectomies have the disadvantages of narrowing the lumen with the long open technique, and leaving loose fragments of intima or athrosclerotic plaques in the lumen with the closed (mechanical stripper) technique (7). Concerning bypass prosthetic grafting, Szilagy et al reported a patency rate of only 40% in 193 cases four years after operation, and Linton achieved only a 6% patency five years after operation (8, 9). The bypass operation with autologous saphenous vein is used most commonly. Here, as always, implanting any prosthesis has many potential problems—not least of which is infection following transient bacteremia. The venous bypass does not have such disadvantages however, 15% to 20% of the patients do not have a satisfactory saphenous or cephealic vein which can be used (10).

Materials and Methods

The ultrasonic device used in this study was the CUSA™ System. It consists of a control and power console with a titanium tip situated within a handpiece and vibrating at ultrasonic frequencies so that tissue can be fragmented and aspirated.

The specimens for this study consisted of two groups of six fresh, unfixed human abdominal aortas with iliac and femoral branches received from autopsies. In the experimental group of six aortas, the technique employed was to gently apply the aspirator tip with minimum pressure to the intimal layer of the aorta. The intima was defined and freed and a plane between the intima and media was developed. The same technique was used in the presence of athrosclerotic plaques. When a calcified plaque was present, since the media was involved, dissection was taken into the media. When it was decided that sufficient stripping had been carried out, the dissection was completed by opening a new line distal to the farthest limit of separation. Again, the ultrasonic tip was applied gently to the intima, with minimal pressure, so that a plane of dissection was opened proximally and continued up into the area previously defined. The endarterectomized core could then be removed en bloc. In the six

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From the Department of Surgery, Bronx Veterans Administration Medical Center and Mount Sinai School of Medicine, N.Y.

control aortas, attempts were made to open up similar planes with the endarterectomy spatula. After intimal dissection was completed, the aorta and iliac vessels were sewn up in order to test for leaks. In the smaller vessels, the ultrasonic tip and endarterectomy spatula were compared in their ability to open a plane from the cut edge of the vessel and continue the dissection.

Results

The CUSA™ System rapidly defined and freed the plane between the intima and media and complete dissection could be made of the intimal core (Fig. 1). The ultrasonic dissection was done without damage to the media and where a plaque was encountered, dissection was simply carried up to it and the plaque was removed with the intima, again without damage to the media (Fig. 2). Heavily calcified plaques were more difficult but simply required a deeper dissection into the media to achieve their removal (Fig. 3). As expected, the procedure was more difficult in heavily calcified aortas, and the intimal layer was broken from time to time. Care had to be exercised in completing the procedure smoothly and

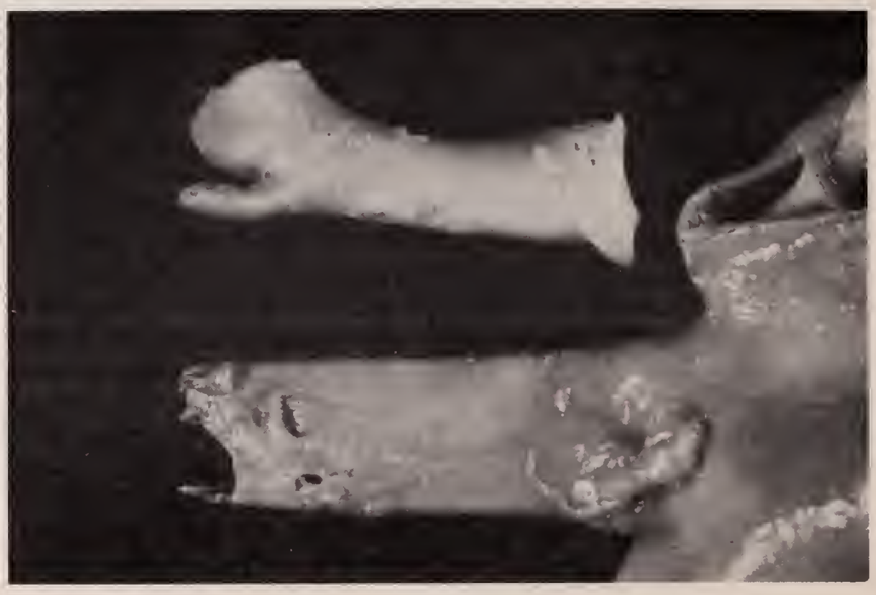

FIG. 1. This photo shows complete shelling out of diseased intima from aorta and major branch by the CUSA™ System, leaving the adventitia virtually untouched.

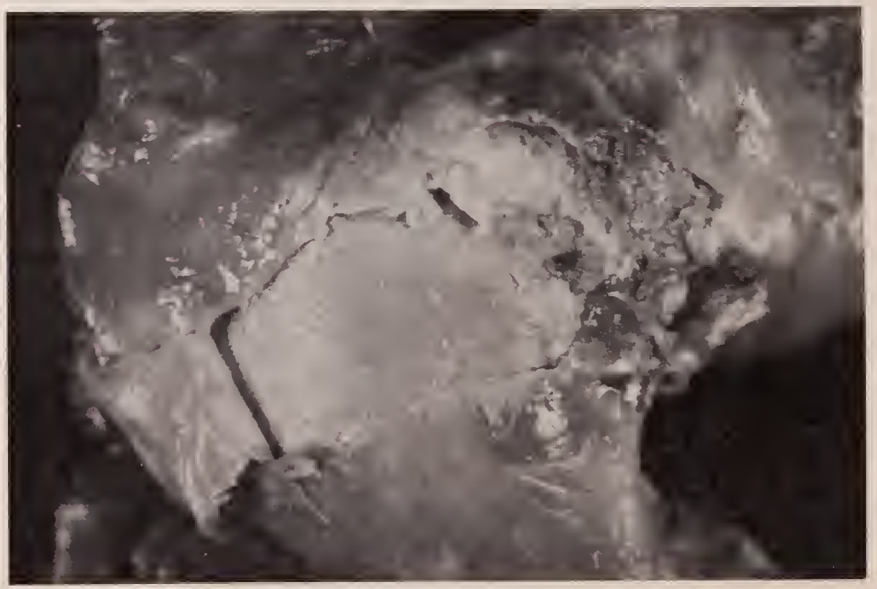

FIG. 2. We demonstrate perfectly smooth media layer underlying an area of intima that was peeled off using the CUSA™ System.

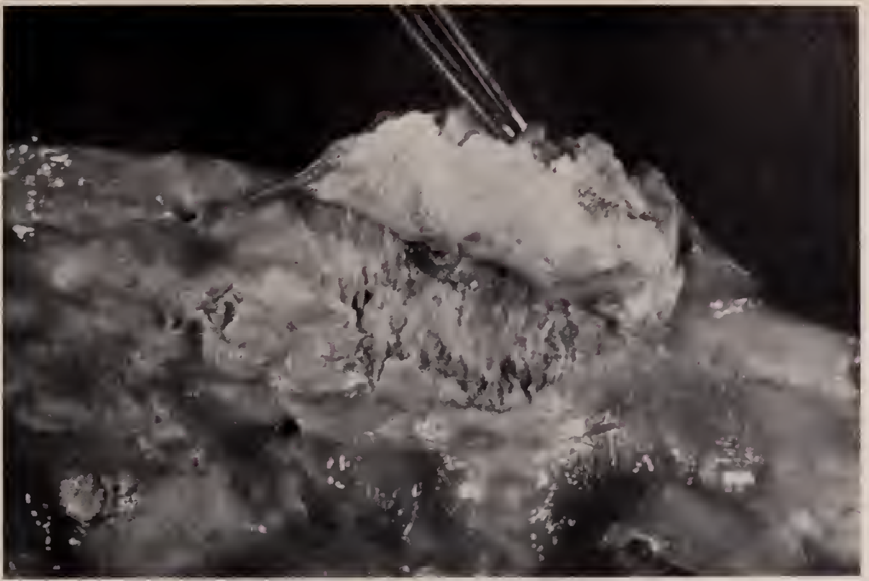

FIG. 3. A calcified plaque was lifted with the intima by the CUSA™ System leaving gently shelved edges. The underlying media has been involved in the athrosclerotic process that after removal, shows a ragged appearance. Further local aspiration is necessary to improve this appearance.

it was always best to commence the procedure, proximally or distally, in relatively uneffected intima. All these aortas were water tight when closed and tested for leaks. We were unable to carry out similar procedures in the aorta with the endarterectomy spatula, because the spatula required a cut edge from which to commence dissection. It was not possible to open a plane directly through intact intima. Also, there was a much greater tendency for the endarterectomy spatula to break out of the plane of dissection than the CUSA™ System.

In the femoral arteries no difference was found in the ability of the CUSA™ System and endarterectomy spatula to maintain a smooth dissection. In both methods, it was found most convenient to start laterally; however, the distal end could be smoothed by a direct approach with the ultrasonic device but not with the endarterectomy spatula.

Discussion

It seems as though the primary difference between use of the CUSA™ System and the endarterectomy spatula for endarterectomies lies in the former's ability to level off the raised, free residual edge of intima. It was also consistently more difficult to initially define the proper plane for the intimal dissection with the spatula. Further encouragement with the CUSA™ System lies in the fact that all the vessels were intact following intimal dissection—a dissection which actually produced a "core" in the aortas, but not in the femoral vessels. A disadvantage of the ultrasonic device was the necessity of a completely opened vessel for the dissection.

Because our initial findings indicate that the CUSA™ System may provide an advance over the established techniques, particularly in decreasing the residual raised intimal edge, work is continuing on this project. Consideration is being given for use of the CUSA™ System in vascular surgery.

Summary

Preliminary studies have been carried out using an ultrasonic system in the development of a new technique for endarterectomies.

Acknowledgements

We wish to thank Mr. John Winkfield and his staff, Mr. Arsenio Torres and Mr. Bruce Seabrook for their assistance on this project.

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City Hospital Center at Elmhurst

Introduction

The City Hospital Center at Elmhurst is a 900-bed facility that provides primary, secondary and tertiary care to a population of one million people. The City Hospital Center affiliation with The Mount Sinai Medical Center began in 1964, with Mount Sinai assuming responsibility for all professional and clinical departments at Elmhurst and all activities involving patient care, teaching and research. Over 200 house staff participate in fully approved training programs in anesthesiology, community medicine, dental and oral surgery, general surgery, medicine and its subspecialties, neurology, neurosurgery, obstetrics and gynecology, ophthalmology, orthopedics, otolaryngology, pathology, pediatrics, plastic surgery, adult and child psychiatry, rehabilitation medicine and urology. Most of these programs are partially or fully integrated with those at Mount Sinai. The medical staff at Elmhurst are all active and participating faculty members of Mount Sinai School of Medicine.

The patient population at Elmhurst is remarkably varied and complements that which is seen at Mount Sinai. The large volume of cases, the diversity of clinical material, the active involvement and responsible participation in patient management by students and house officers, and the presence of highly talented faculty who love to teach have made the educational programs at Elmhurst a challenging, exciting, rewarding experience.

The City Hospital Center at Elmhurst has established itself as a most popular and highly sought after educational and training facility for the Mount Sinai medical students. Over 400 Mount Sinai student rotations, totalling over 1,300 student weeks of training, take place at Elmhurst each year. In addition, many of the Elmhurst faculty partake and contribute to the on-campus teaching activities as lecturers, preceptors and attendings. This past year, a member of the Elmhurst faculty was selected by the Mount Sinai medical students as the first off-campus faculty member to be the recipient of the Excellence in Teaching Award. Other members of our faculty have received singular recognition as the "outstanding attending" in a number of different disciplines, again elected by the Mount Sinai house staff.

The City Hospital Center at Elmhurst directs and conducts, on its premises, the Mount Sinai School of Medicine Fifth Pathway Program. This involves some twenty students. The program has acquired the recognition as being one of the best in the country.

A significant amount of clinical research is conducted at Elmhurst and a large number of scientific publications are generated by the Elmhurst faculty each year.

Stanley G. Seckler, M.D.

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The New York State Medicaid Cost Containment Program: A Case Study and Critique

JONATHAN M. METSCH, Dr. P.H., MARVIN DURELL, and GERALD NIEDZIOLKA

Introduction

Hospital cost containment through control of utilization is a principal concern of the health care industry, particularly as hospital costs have increased at a rate far exceeding overall cost-of-living increases during recent years. In an effort to contain hospital costs, the New York State Department of Health instituted a program in early 1976 that had as its objective, the reduction in the cost of the State's Medicaid Program.

The experience with this program at City Hospital Center at Elmhurst suggests that this utilization review program, premised on achieving cost containment, achieves this objective in a manner inimical to the provision of quality patient care services. This paper will review the New York State program within the historical context of utilization review program development and will document through a case study approach the adverse impact on the delivery of patient care. Finally, the objectives of the Professional Standards Review Organization (PSRO) approach will be presented as more consonant with the historical evolution of utilization review.

Background

Historically, the basis of utilization review and the associated process of medical audit has been peer review. Underlying peer review as the foundation principle for these quality assurance programs, is the notion that any individual physician's or hospital's clinical practice should conform to the standards of practice within the local professional community.

Prior to guidelines set forth under the Medicare and Medicaid programs, utilization review was handled by a committee of the hospital's Medical Board. Typically, utilization review was a process by which charts were reviewed on the basis of random selection or length of stay. Physicians would review cases on an informal basis to check for appropriateness of continued hospitalization. The process was one of judgment based on expert opinion and specific criteria were not used. When the Medicaid and Medicare programs were established, review requirements were introduced in the form of certifications of stay based on physician review at set intervals. Basically, this was a process of admission certification followed by recertification on the 12th and 18th days of hospitalization. If patients stayed for longer periods of time, a utilization review physician had to review the case at 30-day intervals. This type of review at set intervals did not relate to individual patient characteristics; for example, this form of certification and recertification was applied similarly to all patients regardless of their age, physical condition, reason for admission, etc. This was recognized by the Federal Government and after years of pilot studies, the concept of concurrent review and Professional Standard Review Organizations (PSRO's) were mandated by Public Law 92-603.

In November, 1974, Medicare and Medicaid regulations were amended mandating review requirements similar to those proposed in the PSRO legislation. More specifically, review was to be conducted by professionals at specific intervals during an episode of hospitalization, with recertification against norms for a particular disease entity, patient's age, complications, etc. Soon after, New York State mandated that this approach of concurrent review be applied to all patients regardless of reimbursement source.

The most significant element of the concurrent review process is that review of a patient's record by utilization review personnel is based on criteria developed and adopted by the hospital's medical staff. Furthermore, a negative decision can be reached only by physician members of the hospital's Utilization Review Committee (or its designee) and only after the responsible physician has the opportunity to discuss his case and/or supply additional data on the case.

From the Administration, City Hospital Center at Elmhurst, Elmhurst, N.Y. 11373.

It is within this historical context that the New York State Medicaid Cost Containment Program should be assessed.

Description of the Program

In its original form, (See State of New York Department of Health Hospital Memoranda 76-64 (5/13/76) and 76-89 (7/19/76) for official program guidelines.) the legislation establishing the New York State Medicaid Cost Containment Program required that:

1) advance clearance be obtained for all surgery deemed deferrable, that is, surgery that could be delayed for six months without causing disability or pain,
2) certain surgical procedures (tonsillectomy, laminectomy, hysterectomy, etc.) required a second opinion,
3) advance clearance be obtained for any non-emergency hospitalization if a patient was to be rehospitalized for a given diagnosis within a sixty-day period,
4) preoperative lengths of stay were limited to one day unless justification for a longer period was provided in advance of the admission,
5) criteria be met for performing intervention surgery (such as cataract surgery),
6) hospitalization be limited to twenty days unless justification for longer stay could be provided in advance of the expiration of the twenty-day period; however, extensions beyond twenty days could be granted arbitrarily up to ten days and subsequently new requests had to be made, and
7) patient days could be denied as reimbursable on a retrospective basis due to perceived lack of active care documentation in the chart.

In addition, the hospital's discharge planning program had to be clearly documented and progress notes had to be written in a timely manner and reflect active and necessary patient care.

Elmhurst Case Study

City Hospital Center at Elmhurst received notification in September of 1976 that it had been selected as an On-Site Institution and that the State Department of Health would station nurses at the hospital who would perform chart reviews to assure that the care rendered was of an acute nature. They would render opinions, for example, as to the necessity of performing deferrable surgery and granting inpatient hospitalization extensions. A consulting physician would review and certify all negative decisions and could do so without having reviewed the chart–simply basing the decision on the reviewer's assessment. Guidelines in the decision-making process were to be provided by the publication, "Tennessee Foundation for Medical Care."

While the hospital had been getting ready for the on-site program, it was not prepared for the inundation of paper work when representatives from the State Department of Health arrived in October of 1976. Immediately after learning of the program requirements, hospital staff worked to speed up training, to advance the pilot preadmission testing program to full capacity operation, to ready the Utilization Review Office (which was understaffed due to budgetary reasons), and to change its priority from concurrent review to cutback review. Nonetheless, confusion prevailed as physicians completed surgical requests, obtained second opinions and, in some cases, rescheduled surgery. The hospital's losses during the first weeks were minimized since the State had assigned only two nurses to the hospital. In an 800 plus bed institution, where a substantial number of patients are covered by Medicaid or are potentially Medicaid eligible, the State staff members were also engulfed with paper work that could, at best, be superficially reviewed.

Problems over chart availability ensued as State personnel said that they had priority access to records even when the record was needed on the floor to document the ongoing care of seriously ill patients. Patient days were cut in a nondescernable pattern (example: a patient in a body cast, an abandoned infant) because of "lack of documentation." Yet when the hospital requested to see the stated instrument (the Tennessee Foundation for Medical Care) for guiding the decision-making process, it was explained that the on-site staff did not have a copy. Requests for more patient information and records taxed the staff. Nursing reported unidentified and unannounced State administrators reviewing records on nursing units. When written procedural changes did reach the hospital, the effective dates were impossibly close to the date of receipt.

Under the program, cessations of payment are appealable. The appeals process, however, is time consuming with success unlikely. Appeals cannot be made at the local level where the cessation decision is made. A reviewing physician at the State's local offices reviews all appeals which have to be delineated in writing.

Also, at the outset of the program and continuing for almost a year, until the State changed its operating procedures, an appeal had to be filed when the State nurses committed an error of omission (overlooking a key page of the progress notes) or a clerical error (for example, when the State looses an appropriately submitted form). In the event of error, the on-site staff did not have the power to reverse a decision even though it was their's and was acknowledged as such by them.

An injunction obtained by the New York State Medical Society in January of 1977 eliminated the need for second opinions, the 60-day waiver of benefits' clause, and deferrable and intervention surgery requirements. The State circumvented the injunction by requiring prior approvals on elective surgery. On appeal, the injunction was lifted and the second opinion requirement was reinstated, (State of New York Hospital Memorandum 77-91, October 19, 1977.)

Many cessations were due to technical errors. For example, if a form is late, the hospital is denied reimbursement for the number of days of late submission regardless of the need for hospitalization, be it an intensive care day or from a more chronic care unit. Likewise, reimbursement can be and has been denied for an entire length of stay when the contemplated surgical procedure is changed without prior approval, regardless of the necessity for the procedure (State's interpretation of Hospital Memorandum 76-89).

Changes of emphasis seem to characterize the activity of the on-site personnel. For example, after a period of time when there were few denials in the Department of Medicine for other categories, focus shifted to discharge planning and denials increased. State emphasis seems to move to new areas as the hospital manages to reduce or eliminate denials in areas to which the State earlier directed its attention. Thus, the level of denials remains almost constant even as the hospital invests more resources to comply with the program.

While the medical staff has accommodated to writing progress notes to satisfy the needs of nonphysician reviewers, difficulty remains in communicating to the medical staff and, in particular the house staff, the need for timely form completion. Of course, it is realized that a prime concern is patient care; but the connection between this and the documentation required appears to evade many house staff officers. Even the State supports the concept of patient care first. Its officials maintain that they are not directing the physician to treat or not to treat; they are merely informing us what they will pay for and what they will not.

Despite intensive education sessions and repeated written appeals to the medical staff, more than two-thirds of denied benefits during the first year of the program were due to technical errors that are not appealable. The specific examples noted below, highlight the problems experienced at Elmhurst:

- Three cases cut because of delays in surgery and diagnostic testing during the July 1977 blackout.
- The stay of an infant was cut because the 13-year-old mother left it for adoption and the infant's grandmother was vascillating over accepting her daughter's baby because she herself was pregnant.
- Several cases cut in Orthopedics for lack of weekend progress notes on patients in traction, spica casts, etc.
- Forty-four cessations on psychiatric patients who left the hospital on pass for over four hours but not overnight. The hospital was never informed of a four-hour limitation.
- The stay of a semicomatose patient was cut retrospectively even though approvals for continued stay had been granted during the hospitalization. The patient died in the hospital.
- Part of an admission was denied for more than one preoperative day because the physician didn't operate on a patient who had a cold and decided to postpone her surgery and decrease medical risk.
- Preoperative days were denied on an elderly patient who had a psychotic episode prior to the date of cataract surgery necessitating postponement of the procedure.

Structural problems experienced include the following:

- Initially, denials caused by clerical errors on the State's part had to be appealed.
- The State physician is a gynecologist, yet renders decisions about patients under the care of physicians in other specialties.
- As part of discharge planning requirements, the hospital is obliged to call five nursing homes, twice weekly, even when all nursing homes may be filled or the patient requires services that they cannot provide.
- The State nurses were not familiar with Elmhurst procedures, yet were frequently rotated to different hospitals–creating a situation where the hospital was constantly educating new State nurses on its systems.

These observations about the inadequacies of the New York State Program are corroborated in a study done by the Greater New York Hospital Association. The Association study also raises serious questions about the efficacy of duplicative review, due process in appealing denials, discrimination against Medicaid beneficiaries in obtaining hospital care, and the issuing of on-site regulations by the State, thus preempting federal legislation (1).

Analysis of Denials

Table I summarizes the hospital's categorization of the days denied by the on-site inspectors during the three-month period of August, September and October 1977, the percent of days denied in each category and by department, and a comparison of days denied to total patient days by department.

It should be noted that 57.6% of the denials fall into categories which are basically errors of technical noncompliance with the program's requirements on preadmission certification (27.2%), preoperative length of stay (7.7%), and 20-day certifications (22.7%). Payment for days is denied for failure to meet technical/procedural requirements of the program regardless of documentation of the medical necessity of hospitalization.

Preadmission denials are due to the fact that a preadmission request was not approved by the State Department of Health. For the most part, these are technical errors and regardless of medical necessity, the entire

TABLE 1
Days Denied by Category and Service
August, September and October, 1977

	Days Denied by Category								
	Preadmission	Preoperative	20 Day	Charting	Discharge planning	Total days denied	%	Total patient days	% Denied
Surgery	103	36	47	43	—	229	22.8	5667	4.0
Medicine	—	—	6	46	10	62	6.2	14933	.4
Gyn.	139	30	—	10	3	182	18.1	1636	11.1
Pediatrics*	—	—	13	24	7	44	4.4	5983	.7
ENT	23	6	1	—	—	30	3.0	746	4.0
Psychiatry	—	—	122	59	90	271	27.0	13896	2.0
Rehab. Med.	—	—	16	8	—	24	2.4	3412	.7
Other**	8	5	23	107	18	161	16.1	9995	1.6
Total days denied	273	77	228	297	128	1003		56268	1.8
%	27.2	7.7	22.7	29.6	12.8	—	100%		

* Includes Newborn days.

** Ophthalmology, Neurology, Neurosurgery, Urology, Oral Surgery, Orthopedic Surgery.

admission is denied because preadmission paper work was not submitted in a timely fashion. Therefore, these denials cannot be appealed unless it can be documented that the admission was of an urgent or emergent nature. Many of these denials were in gynecology and were the result of admissions planned during a Friday afternoon clinic, with admission scheduled for Sunday or Monday. Even if the proper forms were filled out by the physician, there was technical noncompliance since the State would not have been able to review the case prior to admission.

The State allows one preoperative day unless a request for additional days is granted prior to admission. By the State's definition, extra preoperative days without approval prior to admission are technical errors and can be appealed only through the laborious process of documenting laboratory data, the patient's physical condition, etc.

Denials due to failure to complete a timely 20-day certification represent a unique problem since continued payment can be denied even if the chart is properly documented–simply for failing to fill out a State form in a timely manner. Thus, the prevention of this problem requires clerical support to make certain physicians fill out the form at the proper time, rather than any change in patient care activities.

While 29.6% of the days denied are for charting, this also represents the category for which the greatest percentage of appeals are filed. Here judgment may differ between physician and nurse reviewer on what constitutes appropriate documentation for a given diagnosis. While the nurse reviewers will often deny days for failure to write a daily progress note, this is neither a State Hospital Code, JCAH or PSRO requirement. Nonetheless, these are difficult and time consuming cases to appeal since all such appeals must be accompanied by substantiation from the clinical record.

Denials for discharge planning account for 12.8% of days denied during the study period. Discharge planning is the process by which a patient's social and medical needs are anticipated as soon after admission as possible to assure that the duration of stay in the hospital is limited to acute care requirements only.

Except in extreme cases where the hospital has made no effort to initiate discharge planning, denials for discharge planning reasons represent conjecture on the State's part that discharge could have been anticipated earlier. Experience has shown that while the State will deny days for discharge planning reasons, the State nurses seem to have little understanding of the problems involved in placing a patient in an appropriate, alternate health care setting.

Since the study period, technical errors have been brought under control to a large extent through medical staff education, more stringent controls on the admission process, and increased emphasis on preadmission testing. However, the number of days denied each month remains at almost the same level because the State has increased its denial role in the areas of discharge planning and perceived lack of documentation of active care.

Note that for the study period, a total of 1.8% of patient days were denied and the end result after appeals will be slightly less than that amount. It is questionable whether the investment of resources can be justified given this low rate of denials particularly with the resources the hospital must devote, and get reimbursed for, to technical compliance with the program.

To support this contention that an improper allocation of resources on the State's part is being made by continuing the on-site program at Elmhurst, one can turn to comparative data for the period January to March 1978 on Medicaid denials at New York City Health and Hospitals Corporation institutions with on-site review.

Of the ten Corporation hospitals with on-site review, Elmhurst had the lowest denial rate using a ratio of Medicaid days denied/days approved. The denial experience at Elmhurst was less than 3% while other Corporation hospitals experienced denial rates as high as 50% with an unweighted mean of over 12% (2).

Discussion

PSRO's have the responsibility of ensuring that health care paid for by Medicare and Medicaid is medically necessary, consistent with professionally recognized standards of care, and provided in the least costly setting possible (3, 4). Utilization and cost control is to be achieved through a procedure of self-regulation by physicians with assessments as to the medical necessity, quality and appropriateness of care made on the basis of physician determined criteria (5).

The PSRO provision of Public Law 96-603 created a network of locally based physician groups. The purpose of this network is to review the quality and necessity of hospital care provided to Medicare and Medicaid beneficiaries. It is stated in the legislative requirements that the function would be to promote effective, efficient, and economical delivery of health care services of proper quality. It is further stated that PSRO is organized to make available professional competence to review services rendered. The idea behind this is to utilize the services of local competent physicians and completely foster the concept of peer review. It is incumbent upon the local PSRO's, through its physician organization, to apply professionally developed norms of care and treatment based upon local patterns of practice. It is these norms that are to be the focal point of evaluation and review of the health services rendered. In summary, the PSRO system is a monitoring system aimed at improving the quality of care. It is through an improvement of quality of care and hospital utilization that the system seeks to foster an economical system of health care delivery.

Therefore, the PSRO system of review differs from the Medicaid Cost Containment Program in the areas of norms, peer review, and appropriateness of service. The State system has no peer review, does not use widely developed and accepted norms, and pays insufficient attention to the appropriateness of service.

Under PSRO guidelines, before a definitive decision is made, the physician involved in a case is given the opportunity of explaining his decision. Under the State program, only documentation is reviewed and the critical interaction of the physician within the system is nonexistent.

The New York State Medicaid Cost Containment Program has fostered a situation of defensive documentation equal in degree to the defensive medicine necessitated by the malpractice crisis. For example, house staff are instructed to document patient care to meet State requirements rather, as would be appropriate, from a true quality assurance viewpoint. Increasingly, charts are being prepared to satisfy the on-site team rather than for outcome analysis or continuity of inpatient and posthospitalization care. Medical Board time is inappropriately used to discuss technical compliance with the program while the activities of the Utilization Review, Medical Education, and Medical Records Committees have been diverted from more critical quality assurance issues.

The primary distinction between the PSRO approach and the State program is that the latter does not focus on quality assurance or utilization review–it is a claims review program (6, 7).

Apparently, the State, in attempting to control its Medicaid budget, will deny a number of claims sufficient to reduce its Medicaid outlay (over and above the cost of the claims review program) by targeted amounts. It appears that if the required cost reductions are not forthcoming, more nurse claims reviewers are hired or additional requirements are developed in order to justify the program financially and meet program goals.

Quality or propriety are not the issues. Certainly, it would be more appropriate for the State to meet its budget problems by narrowing the scope of the Medicaid Program, thus limiting expenditures in a simple, straightforward manner. This would in no way help the medically indigent receive care, but it would give the public an opportunity to face the issues squarely, reordering priorities if it so desires.

By obfuscating the issue, by saving tax dollars, by claiming to reduce inappropriate utilization (note again the the majority of denials are technical, not substantive), the quality and scope of services available through Medicaid is reduced indirectly as hospitals reduce budgets in order to cope with revenue reductions. The responsibility for reduced services is suddenly on the hospital, and not the State.

The indirect approach is not only less open, it is expensive. The State started with two nurses at Elmhurst and the hospital with three utilization review (UR) analysts. Since most of the money saved by the State is through identification of technical errors rather than poor utilization or inappropriate care, the game evolves into one of "who can out-document whom?" The State hired more nurses to enhance its ability to identify lack of documentation. Consequently, the hospital hired more UR analysts to insure better documentation. At this writing, the State has five nurses (reduced from seven) and the hospital, six analysts with a request in for the hiring of more. Each side justifies its expenditures for additional staff as being "cost effective." Theoretically, the escalation is endless, a source of employment for inspectors and analysts, with patient care receding into the distance as more and more resources are diverted to claims review. (Since the study period, the percentage of Medicaid days denied has been reduced by nearly half. Without having access to State costs, it is estimated that the savings from denied Medicaid days at Elmhurst can only marginally exceed program costs.)

The only escape from this downward spiral will come when the Department of Health, Education and Welfare, through PSRO's, reasserts its primacy in the area of quality assurance and utilization review. As a note of caution, the PSRO organizational process may also lead to a continuum of outcomes. For example, it has been hypothesized using the literature on innovation theory, that different implementation methods and structures generate different levels of success in meeting federally mandated objectives (10).

The question of whether the PSRO approach is more efficacious than the on-site approach may be answered in the near future by a demonstration project to be undertaken in five PSRO areas. The demonstration project is the result of a New York State Medicaid/federal PSRO jurisdictional dispute over binding authority. DHEW and the State have apparently agreed on the project where "an independent body would establish the demonstration, including selection of various hospital sites, and evaluate the effectiveness of PSRO vis-a-vis State on-site review activity" (11).

In this context, the medical sociologist, David Mechanic, has observed the bureaucratization of medicine and its effect of diluting personal responsibility of the provider, "making it more likely that interests other than those of the patient will prevail" (8). Therefore, PSRO responsibility for quality assurance is much more appropriate than bureaucratic responsibility based on a financial stake in program results (9).

To the extent that appropriate medical practice costs the State more than it is willing to pay, it then should take action to limit its outlay, utilizing an open public process. Only in this way will the public be guaranteed the greatest amount of high quality care for which it is willing to pay.

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Long-term Serial Follow-up After Two Episodes of Heroin-induced Adult Respiratory Distress Syndrome

MANOON LEECHAWENGWONG, M.D., HERBERT W. BERGER, M.D., AND DAMASUS S. JAYAMANNE, M.D.

Abstract

We report long-term serial pulmonary function studies in a 25-year-old man who developed two episodes of adult respiratory distress syndrome (ARDS) following intravenous heroin abuse. Abnormalities in alveolar-arterial oxygen pressure difference and single breath carbon monoxide diffusing capacity (Dsb) reverted to normal within one month while improvement in lung volumes required 15 months. These data indirectly indicated the sequence of recovery, namely, that normalization of gas exchange preceded regression of abnormal lung elastic recoil. The patient developed a second episode of ARDS on reexposure to heroin which suggested the possibility of hypersensitivity to heroin and/or contaminants or a constitutional susceptibility to pulmonary edema as seen in high-altitude pulmonary edema.

Introduction

There have been no previous reports of recurrent heroin pulmonary edema in survivors of the first episode on reexposure to heroin (1). Recurrent episodes of the adult respiratory distress syndrome (ARDS) have been described twice previously but return to normal pulmonary function has not been determined serially (2, 3). Lakshminarayan et al stressed the need for long-term serial follow-up studies especially in nonsmokers to help elucidate features of the recovery pattern (3). We report the first long-term serial follow-up of pulmonary function studies in a nonsmoker who recovered completely from two episodes of ARDS following intravenous heroin abuse.

Case Report

A 25-year-old white male nonsmoker was brought to the Mount Sinai Services-City Hospital Center at Elmhurst on May 23, 1976, comatose after his first intravenous heroin use. The patient was cyanotic and had pinpoint pupils, a blood pressure of 100/60 mm Hg, a pulse rate of 150 per minute, and shallow respirations of less than 5 per minute. After intravenous naloxone 0.4 mg he became alert and tachypneic but continued to be cyanotic. Both inspiratory and expiratory rales were heard. Examination of the heart revealed no murmurs or gallop. Following endotracheal intubation, a large amount of red frothy fluid flowed from the endotracheal tube. He was treated with vigorous suctioning and received assisted ventilation using a volume cycled respirator (Bennett MA-1). The chest x-ray following intubation revealed a bilateral diffuse alveolar pattern with normal heart size. Arterial blood gases demonstrated severe hypoxemia and combined respiratory and metabolic acidosis, for which sodium bicarbonate was given on admission (Table I). Since intermittent positive pressure ventilation (IPPV) and 100 percent oxygen did not lead to significant improvement in arterial oxygenation, ARDS was diagnosed and positive end expiratory pressure (PEEP) instituted. He was also treated with clindamycin and steroids for possible aspiration pneumonia. On the following day PEEP was gradually decreased because of rapid improvement in arterial oxygenation and finally discontinued after 15 hours. He was extubated on the third day. Chest x-ray revealed considerable clearing of pulmonary edema and became normal on the fifth day. Upon discharge after five days arterial blood gases were within normal limits.

On July 10, 1976 he became unconscious following his second intravenous heroin use. He was readmitted to the hospital cyanotic with miotic pupils, a blood pressure of

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From the Pulmonary Section, Department of Medicine, Mount Sinai Services-City Hospital Center at Elmhurst, Elmhurst, N. Y., and Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to: Herbert W. Berger, M.D., Mount Sinai Services-City Hospital Center at Elmhurst, 79-01 Broadway, Elmhurst, N. Y. 11373.

TABLE I
Physiological Data

Time	Mode of ventilation	F_IO_2 %	$PaO_2/(SaO_2)$ mm Hg	$PaCO_2$ mm Hg	pH	Base excess meq/L	PEEP cm H_2O	Total compliance ml/cm H_2O
1st Episode								
Admission	spontaneous	21	23 (14)*	86	6.88	−22		
Hour 4	mechanical	100	38 (58)	57	7.18	−8.5	0	
Hour 6	mechanical	100	67 (91)	48	7.29	−4	10	
Hour 8	mechanical	50	85 (96.5)	34	7.41	−1	15	
Hour 20	mechanical	40	115 (98)	37	7.47	+3	5	
Hour 50	venti-mask	30	98 (98)	33	7.46	0		
Hour 72	spontaneous	21	96 (95)	33	7.38	−4		
2nd Episode								
Admission	spontaneous	21	45 (55)	59	6.98	−19		
Hour 2	mechanical	100	26 (35)	43	7.23	−10	0	25
Hour 2.5	mechanical	100	85 (94.5)	35	7.33	−7	5	38
Hour 4	mechanical	50	86 (94.5)	40	7.33	−4.5	15	61
Hour 24	mechanical	30	84 (95.6)	34	7.44	0	5	42
Hour 48	venti-mask	30	87 (95.6)	31	7.40	−4		
Hour 72	spontaneous	21	91 (96.2)	35	7.33	−7		

* Approximated.

TABLE II
Pulmonary Function Tests After Recovery From the Second Episode of the ARDS

Measurement	Interval after the second episode		
	4 days	1 month	15 months
TLC (percent predicted)	60	80	86
FRC (percent predicted)	64	78	90
RV (percent predicted)	33	59	74
VC (percent predicted)	60	79	83
FEV_1/FVC %	83	89	88
FEF 25–75% (percent predicted)	68	—	—
FEF 50%/TLC (percent predicted)	—	107	89
FEF 75%/TLC (percent predicted)	—	109	80
Raw cm H_2O/L/sec*	3.47	1.12	0.79
Dsb ml/min/mm Hg (percent predicted)	—	105	100
Slope of Phase III (ΔN_2/L)†	—	0.2	0.6
CC/TLC % (percent predicted)	—	81	104
$P(A\text{-}a)O_2$ mm Hg**	15	8	3

* Normal <2.5 cm H_2O/L/sec.
† Normal <0.97 ΔN_2/L.
** Normal <10 mm Hg.

100/60 mm Hg, pulse rate of 148 per minute, and very slow and shallow respirations. After naloxone 0.4 mg was given intravenously, he became alert. He expectorated copious amounts of red frothy fluid and continued to be cyanotic. Arterial blood gases showed severe hypoxemia and combined respiratory and metabolic acidosis, as in the first episode (Table I). He was intubated and PEEP was instituted promptly. The severe reduction in total thoracic compliance seen prior to institution of PEEP improved markedly after introduction of PEEP (Table I). This was accompanied by simultaneous improvement in arterial oxygenation. The optimum level of PEEP was 15 cm H_2O (4). Steroids and antibiotics were not given during this hospitalization. He improved rapidly, as in the first episode. Upon discharge after four days, he had a minimal widening of A-a oxygen pressure difference.

Pulmonary function data are shown in Table II. On the fourth day after the second episode of ARDS there was a marked decrease in lung volumes indicating severe restrictive disease with considerable improvement seen at one-month and 15-month intervals. Although a mild decrease in maximal mid expiratory flow rate (FEF 25-75%) and a slightly increased airway resistance (Raw) probably due to a decrease in lung volumes were seen on initial testing, the forced expiratory volume at one second to the forced vital capacity ratio (FEV_1/FVC) was normal and remained so subsequently. This together with normal flow-volume ratio at mid and low lung volumes and normal single breath oxygen test (normal phase III and closing capacity) were taken as evidence of normal airway function. The alveolar-arterial oxygen pressure difference returned to normal within one month. Single breath carbon monoxide diffusing capacity (Dsb) at one month and 15 months was normal. A slight decrease in residual volume (RV) was the only abnormality in pulmonary function noted after 15 months. At 15 months after the second episode of ARDS he remained asymptomatic, had a normal chest x-ray, and had refrained from heroin abuse.

Discussion

ARDS is a multifactorial form of acute pulmonary injury leading to extreme tachypnea, refractory hypoxemia, reduction in lung compliance, and diffuse alveolar densities on chest x-ray (5). With prompt therapy about half the patients survive (6). Following recovery, the magnitude of residual damage may vary (2, 3, 7–11).

Available data suggest that most patients have minimal functional abnormalities several months after recovery. In two instances of recurrent ARDS pulmonary function returned to normal at 12 and 18 months, respectively; however, the sequence of recovery was not determined (2, 3).

Our patient had some unusual features. He developed ARDS on his first use of heroin. Clinical recovery was rapid after therapy using PEEP, supplemental oxygen, steroids, antibiotics, and sodium bicarbonate. Arterial oxygenation returned to normal in four days. A similar episode following his second heroin use approximately seven weeks later was promptly treated as in the first episode except that steroids and antibiotics were withheld. Clinical recovery was once again rapid. On the fourth day after the second episode of ARDS he had only a minimal widening of A-a oxygen pressure difference despite marked decrease in lung volumes. A month later the A-a gradient and single breath diffusing capacity were normal. The slow improvement in lung volumes indirectly indicated the sequence of recovery, namely, that ventilation-perfusion abnormalities responded to therapy long before improvement was noted in abnormal lung elastic recoil. Complete recovery after two episodes of ARDS was probably due to good patient management, avoidance of oxygen toxicity during the acute phase of ARDS, young age, previously normal state of the lungs, and restraint from further heroin abuse. Frand et al reported sequential pulmonary function studies following one episode of heroin-induced pulmonary edema (12). The sequence of recovery is similar to that in our patient.

The pathogenesis of heroin-induced pulmonary edema is not clear. The fact that our patient developed a second episode of ARDS on reexposure to heroin suggested the possibility of a hypersensitivity reaction to heroin and/or contaminants, or a constitutional susceptibility to pulmonary edema as occurs in high altitude pulmonary edema. Hultgren et al reported a marked degree of pulmonary hypertension in subjects with a previous history of high altitude pulmonary edema on reentry to high altitude (13).

Acknowledgments

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Immediate Obturation of Neonatal Cleft Palates

JEROME A. MARKOWITZ, D.D.S., ROGER G. GERRY, D.M.D., and ROCHELLE FLEISHNER, M.A.

Abstract

Immediate treatment for the newborn child with a cleft palate has often been overlooked by those responsible for his treatment. This procedure involves the placement of a simple intraoral obturator fabricated and inserted within hours after birth. This obturator effects a reduction in traumatic family tension; a positive feeding program; a less complex surgical palatal closure and a substantial improvement in speech.

Introduction

Immediate treatment for the neonate with a unilateral or bilateral cleft palate has often been overlooked by those responsible for the implementation of these procedures. The incidence of this orofacial abnormality is one in every 750 births and pediatricians, as well as other involved specialists, seem to be unaware of the availability of immediate obturation and its concurrent benefits (1). This treatment involves the placement of a simple intraoral obturator, essentially an acrylic baseplate, fabricated and inserted within hours after birth. The technique reported in this paper has been developed independently of any prior research. Nevertheless, several authors have discussed the concept of treatment for the neonate with cleft palate. Oliver of Montreal constructed a removable appliance to prevent collapse of the palatal segments in the newborn child with cleft lip and palate (2). Rosenstein of Chicago writes of a new concept in early orthopedic treatment of clefts to assist in the functional improvement and esthetic alignment of the dentition (3). Spira of Houston discussed the early use of an appliance, passively placed within the first week or two after birth, in conjection with the use of the Nuk Sauger nipple (4). This early plan of maxillary orthopedics in cleft palate patients reflects a changing trend in the management of these deformities. Pruzanksy cited growth studies to substantiate the benefits of early orthodontic intervention following the eruption of the deciduous dentition (5). McEvitt described the insertion of a Silastic appliance over the palate to prevent the collapse of the maxillary segments (6). C. K. McNeil in his text *Oral and Facial Deformities* envisioned these early treatment modalities in the 1950's (7). Despite acknowledgement in the literature of the importance of early intervention, most treatment has been restricted to procedures carried out after the child is days to weeks old. It would appear that little support has been generated and little work has been reported on the treatment of the newborn within hours of birth, a technique which considerably enhances the benefits of this type of management.

Materials and Methods

In the City Hospital Center Mount Sinai Services Dental and Oral Surgery Program, we have treated and followed eleven cleft palate patients born during the past four years. Six had full unilateral cleft of palate and lip; one had a full bilateral cleft of palate and lip; and four had varying degrees of palatal cleft with intact maxillary ridge and no lip cleft. Nine were fitted for obturation within the first twenty-four hours of birth; one was fitted seven days later because of physical problems more serious than a cleft palate; and one was fitted seventeen days after birth. The latter was born at another institution and referred for treatment.

Technique

As stated earlier, the treatment involves the placement of a simple acrylic intraoral obturator fabricated and inserted within hours after birth. The technique is simple and straightforward and requires only a meager armamentarium. A soft, white wax sheet dipped in warm water is molded in moments to conform to an appropriate sized tray with handle. This is trimmed and carved with a sharp knife, then redipped in warm water to regain maximum pliability, replaced in the infants mouth, and

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From the Department of Dental and Oral Surgery, Mount Sinai Services, City Hospital Center at Elmhurst, Elmhurst, N.Y. 11373.

with slight molding by finger pressure, the tray is fabricated. This tray is now dipped into chilled water to maintain the established contours. Holes are punched in several areas through the wax tray to create a locking medium for the final impression material. A small amount of quick-setting alginate, mixed with tepid water to effect a more rapid set, is sparingly placed into the wax tray. A bit of gauze may be placed into the palatal cleft to block out the soft material from becoming entrapped in the undercuts of the defect. During the time of the impression, the infant is held in an upright position. The material remains in the infant's mouth for less than thirty seconds. The nasogastric tube, placed in most cleft palate babies, remains during the impression procedure and is removed at the time of insertion of the finished appliance. This usually coincides with the first oral feeding. Inasmuch as the insertion of the initial obturator is but a first step leading up to the final surgical closure of the palatal defect, it is necessary to fully explain to the mother the insertion, removal, and cleansing of the prosthesis, as well as the details of follow-up treatment.

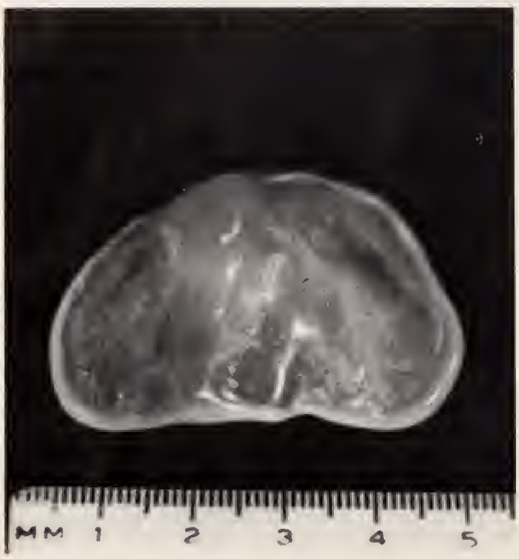


FIG. 1. Intraoral acrylic obturator.

Intraoral growth necessitates regular examination (weekly, within the first two months, twice a month thereafter until the time of surgical intervention). The initial appliance must have the peripheral flanges reshaped, extended and relieved to allow for maxillary growth. Dependent upon the rapidity of this growth, new impressions and appliances may become necessary at six to eight week intervals. The depth of defect is not incorporated into the design of the prostheses. However, selective area contouring of the appliance may be used to direct the segment or segments toward or away from the mid-line (Fig. 1–4).

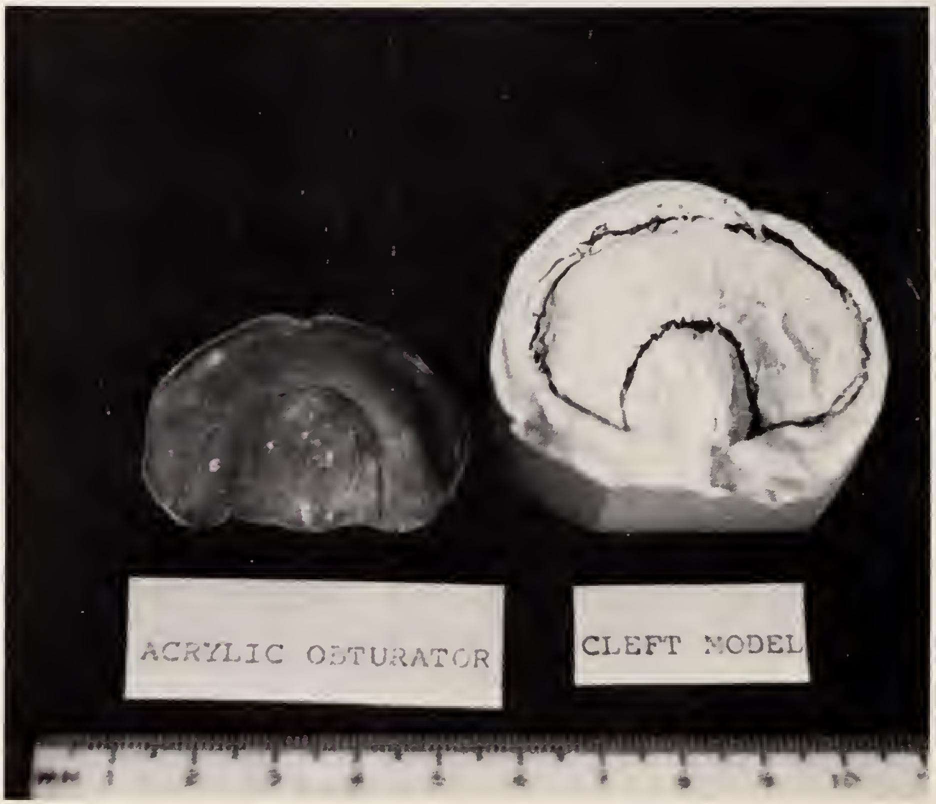


FIG. 2. Neonatal obturator and model.

Results

The ease of acceptance of the appliance by the nine infants was remarkable. From the time of insertion of the prostheses there was no apparent discomforture and normal feeding was possible with a standard nipple. Neither the aspiration nor the swallowing of the prosthesis was ever a factor. All children treated with obturation within the first twenty-four hours were discharged from the hospital within the usual time span for healthy children. This four to seven day stay differs markedly from the prolonged hospitalization of the nonobturated cleft palate baby and, therefore, the financial burden to the parents is reduced. A large, healthy infant born with cleft palate and no other adverse physical findings could be expected to remain five to eight weeks because of difficulties with feeding. A smaller baby with similar physical findings may have been hospitalized as long as three to four months.

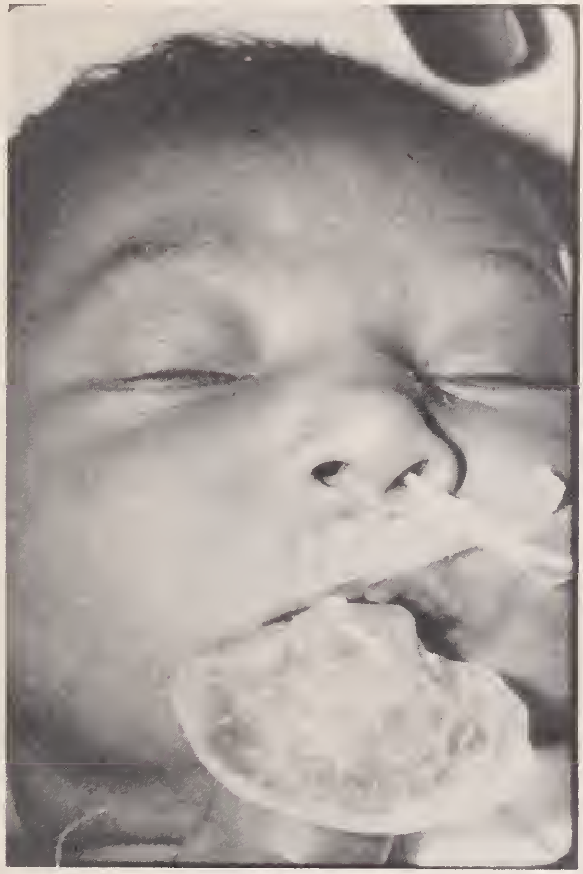


FIG. 3. Obturator about to be inserted, eight hours after birth. Nasogastric tube in place.

One child died at one month of age from an unrelated renal disease, but for that month was fed normally with the obturator in place. One baby was discharged and never returned for further treatment. One infant, a Down's Syndrome baby, died six days after birth.

The eight remaining children were followed at routine intervals and all exhibited continued acceptance of the prosthesis. The parents also were at ease with the handling and cleaning associated with feeding. Actually, the use of a standard nipple and bottle instead of the overlong Lambs nipple, or obturator nipple, reduces the anxiety and trepidation of the parent. When a baby exhibits a growth and development level within standard and acceptable normal limits, and can be handled and fed within the normal program, obviously the involved parents are also at ease with themselves and their child.

All the babies showed maxillary growth in all dimensions, but within the cleft area growth was more rapid. By the fourth or fifth week all defects showed a minimum of twenty to twenty-five percent filling in with soft tissue in both superior and lateral aspects.

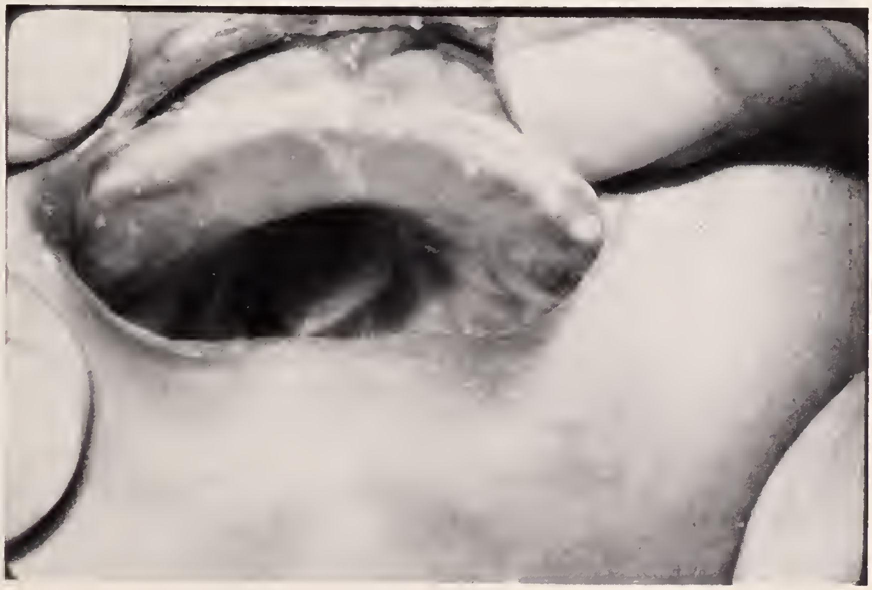


FIG. 4. Obturator in place. Nasogastric tube is visible through clear acrylic.

At the time of the third appliance being introduced, usually by the sixth to the eighth month, fifty percent and more of the defect was closed.

The children who required lip and/or nasal repair had these surgical necessities treated from one week to twelve weeks after birth with no untoward results.

For all but one child, babbling sounds, crying sounds, and words when spoken, sounded far less nasal to the speech pathologist than the typical cleft-palate sound of the unobturated baby.

The following case history is representative of all the above situations:

Case Report

A male infant was born with a unilateral complete left cleft lip and palate. The mother's two other children were born with other defects - one, respiratory and one, renal. When the mother was informed of the cleft, she rejected the infant by refusing to look at him and stated that she would not take him home. The neonatal appliance was introduced and the mother was informed of this procedure. The essentially normal feeding and subsequent treatment plan was also discussed with her. The procedure and discussion were reinforcement enough for the mother to overcome her initial reaction. She was able to take her infant home within the normal range of time. This was very different from the extended period of hospitalization her two other children had undergone. She understood that the orofacial defect was being treated and would be partially eliminated and this knowledge caused a total reversal of her feelings. For the first six weeks, the mother and child came for necessary adjustment and changes of the prosthesis at weekly intervals. The mother never ceased to comment that her child was becoming lovelier and chubbier. At three and one-half months of age the child weighed more than eleven pounds and was ready for lip and nasal reconstruction.

The plastic surgeon insisted on a three-week respite from the use of the appliance. The mother, for that three week period, fed her son in an upright position and she was relieved when the obturator could be replaced. All the joy of feeding was lost when she knew she could hold her baby only in a simple upright position.

It was noted, prior to the lip surgery, that 20% of the cleft of the palate had closed. At the time of the new appliance, three weeks postoperatively, it was noted that more of the defect had filled in. With each subsequent change of the appliance, up to the age of ten months, the amount of cleft opening was continually reduced to the point that only 25% of its original cleft size remained (Fig. 5-5a).

It is contemplated that final surgical intervention for full closure will be accomplished at 14 to 16 months of age. Based upon the amount of closure that has already occurred, the ease of surgical repair should be most enhanced.

Since the lip and alar reconstruction, the mother's only comment was "God, he's a gorgeous kid!"

Uniformly positive results have demonstrated a pattern of easy acceptance by both child and parent, an essentially normal feeding program, a decided reduction in the size of the defect without diminution of maxillary growth, an improvement in the cleft palate sound toward more normal speech, a positive reinforcement of the family structure, and ancillary benefits toward the well-being of the child.

Discussion

Cronin states that "we have to take advantage of the quite dramatic rate of maxillary growth within the first months of life, not interfere with it, and avoid or delay any procedure which might endanger regular development" (8, 11). Although the literature is oriented toward the question of benefits arising from the use of this obturator as an orthodontic appliance, and we wish to acknowledge these positive findings, it must be stressed that this management of the neonate with a cleft palate defect has shown evidence of significant benefits on a broader level. Of primary importance in early obturation is the elimination of the upward protrusion of the tongue into the defect area, thereby creating a more normal tongue location (Fig. 6, 7). Having removed the major obstruction, palatal shelf activity can be expected to occur. Although we cannot completely explain why we find the amount of defect closure that does occur, a probable explanation is that the pressure resulting from the outer flange of the obturator and the normalization of pressures following lip repair (when indicated) stimulated the palatal soft tissue growth that was interrupted during fetal growth. Perhaps a catch-up pattern exists.

It has also been observed by the authors that seemingly micrognathic mandibles in the neonate, not necessarily associated with the Pierre Robin syndrome, seem to assume a more normal relationship in size within a matter of months. We can hypothesize that with the tongue and associated musculature in a more normal functional relationship, the pressures exerted do assist in the normal facial and skeletal contouring.

E. Kelley discussed feeding the cleft palate child (9). She stated, "there is one certainty that all must concede in our mutual concern for the cleft palate child. Before the plastic surgeon can perform his first operation, before the orthodontist can prescribe the first corrective measures, before growth and development progresses to a time of concern for speech production, before everything

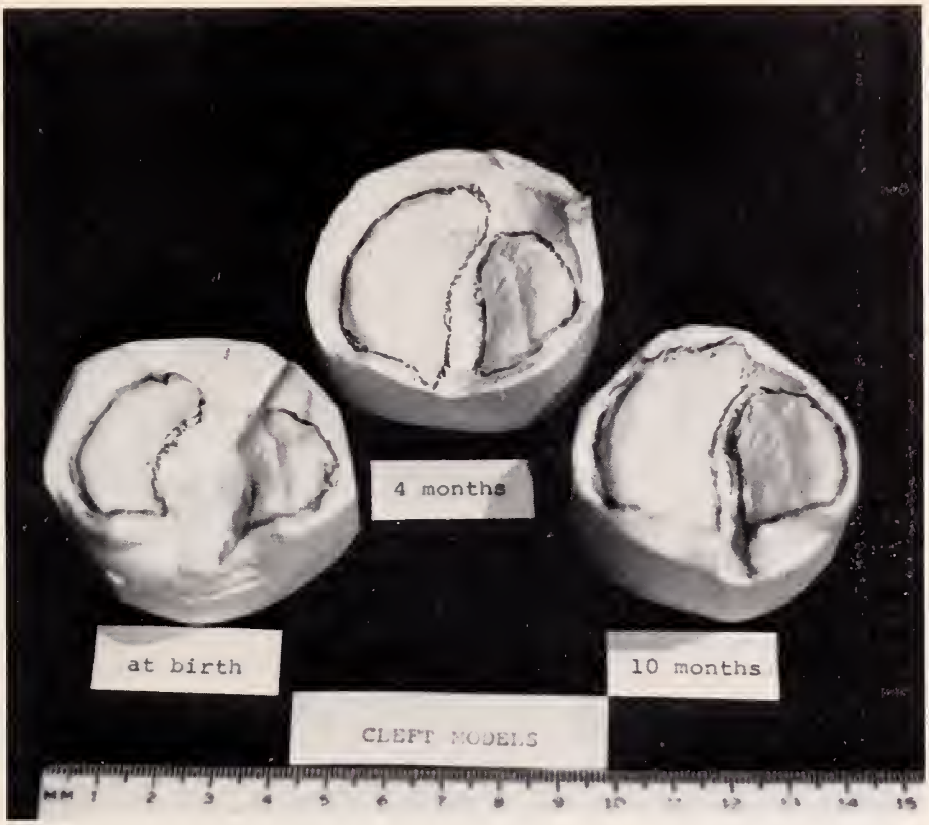
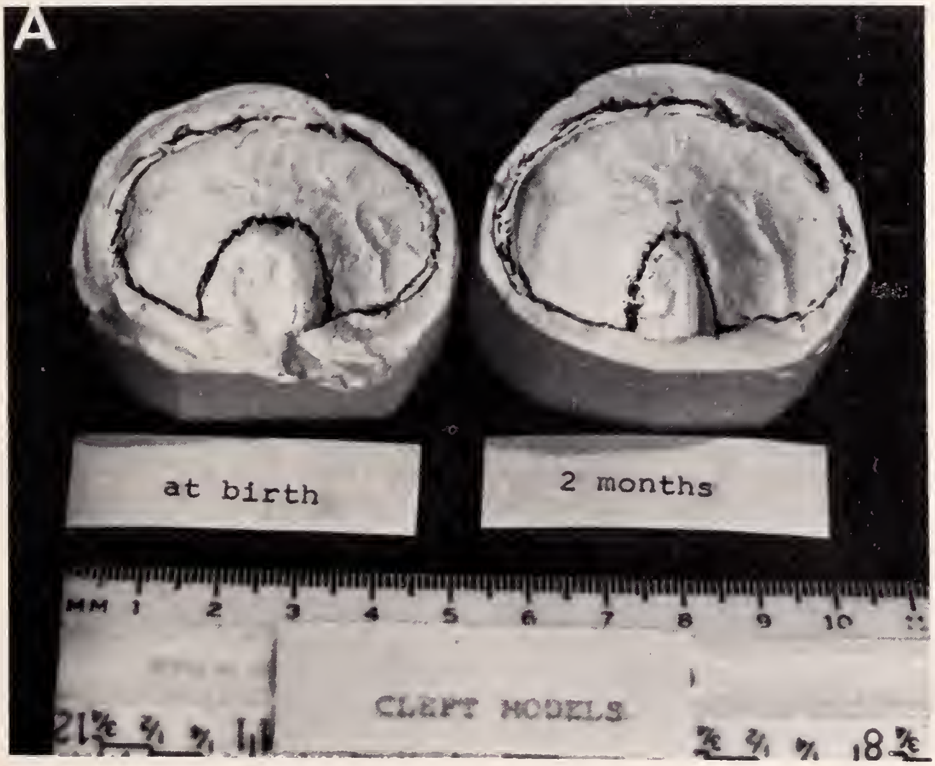

4 months
at birth
10 months
CLEFT MODELS
MM 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

FIG. 5. Cleft closure and segmental alignment. FIG. 5a. Cleft reduction.


A
at birth
2 months
MM 1 2 3 4 5 6 7 8 9 10
CLEFT MODELS

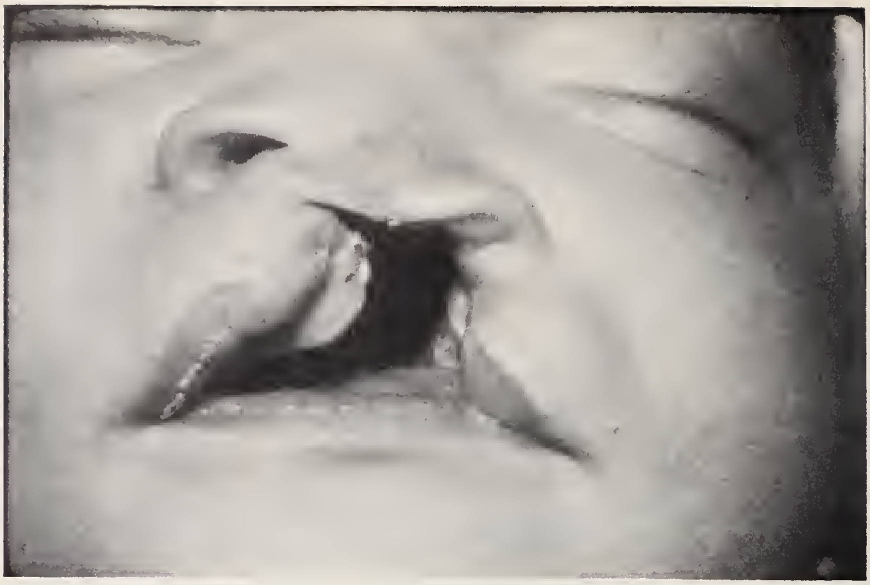


FIG. 6. Unilateral cleft, day of birth.

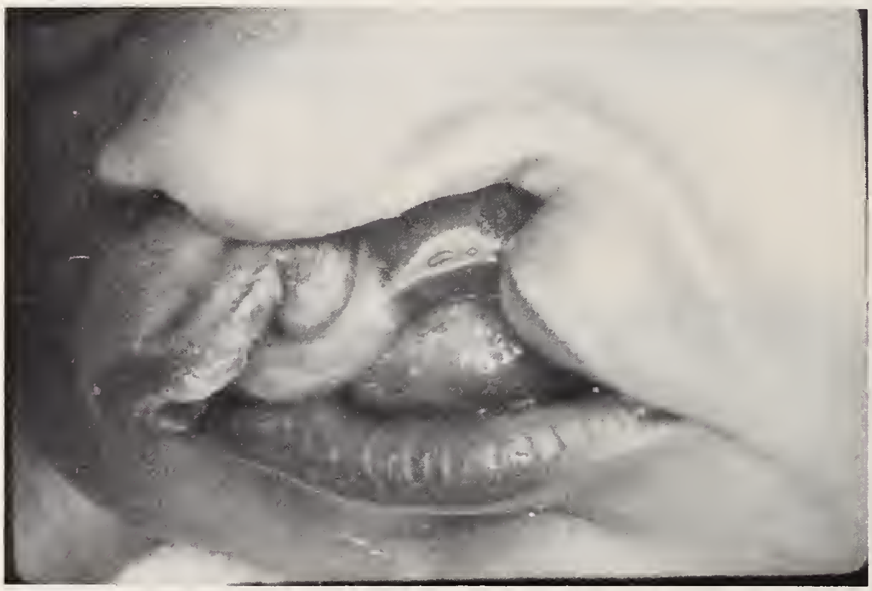


FIG. 7. Prosthesis inserted day of birth. Tongue in normal position.

else, this baby must survive. Unless he reaches a state of adequate nutrition, the outlook for successful management by any specialty is diminished. Caloric, fluid and chemical balance is best realized through the baby's regular oral intake of a normal diet." Feeding an infant should be a time of relaxation and enjoyment for both parent and child. Although feeding techniques have improved over the years, the unobturated infant still has the oral defect and feeding must proceed with care.

The intraoral device under discussion, mechanically blocks off the cleft, providing the infant with an artificial palate against which he can suck normally. This produc tion of a functional seal, creating a negative pressure i the oral cavity allows the mother the choice that mos mothers with normal children have, she can breast fee or bottle feed.

The professionals' responsibility to the cleft palat child and the family involve emotional as well as physica implications. The emotional impact of the cleft palat child on the family can be quite a handicap in itsel Because we live in a society where physical appearanc is stressed, the birth of a child with an orofacial deformit can have a catastrophic effect on the parents. However, it has been the authors experience that, when parents discover something immediate is being done for their baby, the traumatic impact is reduced.

Another potential benefit of the appliance is in the area of speech. Westlake and Rutherford discussed aspects of cleft palate speech that were based on studies done by Bzoch, Olson and Star (10). Learning to manipulate the articulators develops in the stage of preverbal vocalization. During this stage, the child begins to perceive the sounds he makes. Part of this perception involves tactile and kinesthetic sensations associated with movements of the articulators. Babbling, which normally begins at around six months, is included in the preverbal stage. Here, the child seems to produce sounds deliberately and he finds these sounds interesting and useful. As a group, cleft palate babies begin to babble at around nine months, a substantial period of delay.

Olson found that cleft palate and normal babies produced the same number of identifiable speech sounds. However, the sounds of normal children were more diversified. Normal babies used the high front vowels while the cleft palate children used more back vowels. As for consonants, labial and lingual, fricative and plosives were used early by the normal infants while cleft palate children used mostly glottal sounds. The cleft palate children, in other words, used the posterior part of the oral cavity, for the simple reason that that part of the vocal tract was not affected by the deformity.

We have observed that the children fitted with the appliance did not exhibit characteristic cleft palate ounds. Their sounds were clearer and more diversified han could be expected of unobturated cleft palate infants of similar age. Although it is too early to make a definitive udgement as the effect of this procedure on the speech production of cleft palate children, it does appear to nhance the early development of normal speech sounds.

Summary

While each of the positive results may not of itself be f major importance, the sum total is impressive. When a procedure as simple as the immediate obturation of a newborn can produce so many beneficial results, it would seem that this information should be made available to the practitioners involved. The pediatrician who first is aware of the problem, the plastic surgeon, the dentist, the social worker, the psychologist, the speech and hearing pathologist, etc. (who should all be part of the cleft palate team), must maintain a multidisciplinary treatment plan from the day of birth to and beyond the ultimate surgical closure of the defect. If the obturation of the neonate can effect a lessening of traumatic family situations, a positive feeding program, a less complex surgical procedure, and improvement in speech, it is incumbent upon the informed specialists to set in motion the early machinery of communication and treatment.

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Competency for Trial: The Competency Screening Test in an Urban Hospital Forensic Unit

LEO SHATIN, PH.D. AND STANLEY H. BRODSKY, M.D.

The problem of psychiatric evaluation for competence to stand trial has been fully explored in recent publicaions (1, 2). A competency screening test (CST) was developed by Lipsitt, McGarry et al as a rapid screening nstrument for competence to stand trial (3, 4). It is a sentence completion test with 22 items that elicit completion responses pertinent to the legal criteria for competency (understanding the nature of the legal process, recognizing the nature and consequences of the charge, and the ability to assist legal counsel in own defense). Each completion response is scored zero, one or two (4). These are summed to yield a total test score with critical points at 20 and 21 where ≧ 21 signifies competence and ≦ 20 signifies incompetence. The scores may range up to and including the maximum of 44. The original test validation was conducted at Bridgewater State Hospital with men whose median age was 30 years, whose educaional level was 9th grade, and whose average full scale Wechsler Intelligence Quotient (IQ) was 92 (3).

Problem

1. Is the competency screening test routinely applicable o female patients who are court remanded for compeency evaluation in a locked ward facility of a large municipal hospital? How do its results compare with omplete clinical psychiatric evaluation for competence?
2. What is the relationship between the test and verbal intelligence?

Method

The competency screening test (CST) and the Wechsler verbal intelligence scale were administered to a serial roup of unselected women (N=21) who were tested in he course of their clinical psychiatric evaluation for ompetence to stand trial, in the Forensic Service of The City Hospital Center at Elmhurst (2). Clinical psychiatric evaluations included intensive psychiatric examination, hospital observation, and background histories.

The original CST was administered to each patient; however, the male names in the sentence stems were changed to female (that is, "Bill" became "Jane") since this subject population was female. The scoring criteria were as published in the test handbook (4). In most of these test administrations the sentence stems were read aloud by the patient, or in some instances by the examiner, to ensure verbal understanding although the examiner did not explain the meaning of the words. The patient wrote down her sentence completions except in those few instances where she could not write and the examiner did so for her.

The full Wechsler verbal intelligence scale (information, comprehension, digit span, arithmetic, similarities, and vocabulary) was administered to all but one patient who received the Otis intermediate self-administering test of intelligence, a paper-pencil test.

The final clinical psychiatric evaluation judgment of competency in each case was made by an experienced forensic psychiatrist who had multiple interviews with the patient, observed her ward behavior, had access to all nursing notes and observations, was informed of the case history data, and who made full use of professional social services. The forensic psychiatrist was also aware of any psychological test results for each patient other than the competency screening test.

Sample

Patients remanded for competency evaluation were referred serially for psychological testing, except several women who were unable to comprehend English and were thus excluded from this subject series. The study sample consisted of 21 patients with a median age of 32 years (Q_1=20.1, Q_3=35.8), and with a median education of the 11th grade (Q_1=9, Q_3=12). Twelve were black or hispanic and nine were white; 19 were born in the U.S.A.

From the Department of Psychiatry, City Hospital Center at Elmhurst, Elmhurst, N.Y. 11373.

and two were born elsewhere. Seven said they were housewives; those that had worked had done so in unskilled or marginal employment areas. Median length of stay for this period of competency observation in Elmhurst was 31 days ($Q_1=25.2$, $Q_3=43.8$). Accuracy of the stated educational level was open to doubt since this figure was often supplied only by the patient and not necessarily corroborated. The criminal charges varied, ranging from harassment or bail jumping, through trespassing, assault, criminal mischief, arson, robbery, possession of stolen property, homicide, or attempted homicide.

Results

Two patients did not cooperate fully with the intelligence testing. One of these had some college and was estimated to be of high average intelligence. She was therefore assigned a high group rank for intelligence. The other was excluded from computations involving relationships with intelligence. Three refused some CST items or gave unrelated or excessive "don't know" responses. These items were scored in the "incompetent" direction and generated lower rank scores.

The median average Wechsler verbal I.Q. was 78 ($Q_1=72$, $Q_3=93$), high borderline range. Four patients scored mildly retarded, six borderline, four dull normal, six average, one unknown (noncooperative). This was substantially lower than the average full scale Wechsler I.Q.=92 of the original Bridgewater State Hospital experimental group, although the discrepancy or difference was probably heightened by the inclusion of performance subtests for the latter group (3). In this type of population, verbal intelligence tends to be lower than performance-type intelligence.

The median average competency screening test score of our subject group (N=21) was 18.5 ($Q_1=8.5$, $Q_3=25.25$), which compared closely with the original Bridgewater experimental sample whose mean test score was 18.45 (2, 3). Ten patients were judged competent by this screening instrument, 11 were judged incompetent.

The final clinical psychiatric evaluations of competency for the Elmhurst group (N=21) by the forensic psychiatrist were in the ratio of 12 competent/9 incompetent.

Table I classifies all patients' scores on the CST (≧21 signifies competent, ≦20 signifies incompetent to stand trial), and further subdivides them according to their classification as competent or incompetent by the clinical psychiatric evaluation. Seventeen were consistently classified by the two methods, four were inconsistently classified. This constituted 81% agreement that compared most favorably with the original experimental study (2, 3).

TABLE I

Classifications of Competence by Competency Screening Test and by Clinical Psychiatric Evaluation, According to Primary Diagnosis

Clinical Psychiatric Evaluation	Competency Screening Test Scores				Totals
	Low (≦20)		High (≧21)		
	Incompetent		*Competent*		
Incompetent	Schizophrenic	8	Schizophrenic	1	
		8		1	9
Competent	Schizophrenic	1	Explosive personality	1	
	Inadequate personality	1	Schizophrenic	6	
	Mental retardation	1	Personality disorder	1	
			Depressive neuroses	1	
		3		9	12
Totals		11		10	21

A Chi Square test of homogeneity was conducted for the two procedures. This showed a statistically significant association (Chi Square = 6.40, $P < .02$) between competency screening test scores and clinical psychiatric evaluations of competency.

The greatest single discrepancy in Table I was the quadrant where three patients were classified "competent" by the clinical psychiatric evaluation but "incompetent" by the competency screening test. The CST yielded more "positives," a qualification appropriate to its use as a screening instrument since when it errs it tends to err on the conservative side and calls for follow through by the more comprehensive clinical psychiatric evaluation.

The majority of our patients carried primary schizophrenic diagnoses (16 of 21 patients), but the grid discrepancy in Table I between competency classifications involved only two schizophrenics along with one mental retardation and one inadequate personality. The schizophrenic diagnosis more often seemed to accompany a clear evaluation of "incompetent" by both procedures. This was similar to Lipsitt et al's finding (3). However, the diagnosis of schizophrenia per se is distinctly insufficient to serve as the single criterion for competence.

The four patients who were inconsistently classified by the two methods did not seem different from the others in the quality of their criminal charges: one arson; one homicide; one assault 2°; one robbery 1°.

We investigated the hypothesis that verbal intelligence was related to the results of the clinical psychiatric evaluation, for the latter did require some knowledge of court procedure. But a Chi Square test of homogeneity gave no reason to reject the null hypothesis for this population sample (Chi Square = .03, $P > .90$). Indeed, the patient with the lowest intelligence score, verbal I.Q.=60, was classified competent by clinical psychiatric evaluation while other patients with higher intelligence scores were adjudged incompetent.

We investigated the hypothesis that verbal intelligence was correlated to the competency screening test, since the CST seemed to require some cognitive ability both in approach to the test format and in substantive test content. If a significant relationship did exist, then use of the competency screening test would require certain precautions concerning the intellectual level of the testee and could not be used routinely in all cases to explicate the problem of competency in a municipal hospital forensic facility such as ours. We computed the rank order correlation between Wechsler verbal I.Q. and the competency screening test scores. The low positive correlation (Rho=.24) did not attain statistical significance ($N=20$, $P < .30$). But a further test, the Chi Square test of homogeneity between the Wechsler verbal I.Q. and the competency screening test, did attain statistical significance at a moderate level (Chi Square = 4.25, $P < .05$). These conflicting statistical data do not allow for firm conclusions concerning significant relationships, but they do suggest that a positive trend is present. Although further investigation is required, there is no reason to substitute intelligence testing for the sentence completion test in this group as a whole.

These results should not be construed as criticism of the screening evaluation test, for its author applied the test only to the intellectually average or better, and made no claims about its use at below-average intellectual levels.

The median average hospital stay for this group of patients in the forensic service was 31 days ± 9.25 days (semi-intequartile range). Their psychiatric status did not necessarily remain static during this period. The clinical psychiatric decision about competency was more likely to be related to their status in the later phase(s) than in the earlier phase(s) of stay. Hence, the degree of correspondence between the clinical psychiatric evaluations of competence and the psychological test findings (verbal I.Q. and sentence completions), conceivably might have been influenced by the time in their stay (early or late) when the psychological tests were administered. The mean time difference between the date of the clinical psychiatric decisions regarding competency and the date of psychological testing was computed at 17.5 days. This time difference seemed unrelated to any discordance in the results. The mean time discrepancy for all concordant findings, between the sentence completion test and the clinical evaluative decision was 17.7 days; and for the few discordant findings, the time discrepancy was 16.8 days. This was not significant. The study sample yielded no evidence that a time lag between the clinical psychiatric evaluation and the sentence completion testing during the course of hospital stay and evaluation, led to any discordance in findings of competency by the two difference procedures.

Discussion

Problem one was answered affirmatively. The competency screening test did seem routinely applicable to the type of female patient remanded to the forensic service of a large municipal hospital for competency evaluation. Its results compared favorably with the clinical psychiatric evaluation criterion.

Problem two was not definitively answered. There was a suggestive inverse relationship between competency screening test and verbal intelligence, but this was not firmly demonstrated despite the wide intelligence range of the subject group (broad "range of talent"). However, it was clear that intelligence level, within the range of talent of this group, did not influence the outcome(s) of the clinical psychiatric evaluation of competence.

Intelligence per se does not serve as a sufficient guide for competency evaluations. Even in the lower ranges, as in our sample, it does not displace the applicability of the competency screening test of sentence completions.

The time lag differential between psychological testing and the final clinical psychiatric evaluation in the forensic service did not seem to create discrepancies between competency screening test results and clinical psychiatric evaluations.

The forensic psychiatrist who evaluated these patients had taken special training in competency evaluations that included a focus upon topics of interview that were quite similar to those of the competency screening test. The psychiatrist included these in his own interviews with competency patients. This probably contributed to the considerable congruence of findings between clinical psychiatric evaluations and competency screening tests in the present study. It is not common in cross-validations of psychological tests that the second cross-validation study attains validity levels as good as or better than the original test validations—which was the actual case in the present study.

Summary

A serial group of 21 unselected female patients referred to the forensic service of a large municipal hospital for comprehensive clinical psychiatric evaluation to determine competency to stand trial, was concurrently but independently tested with Wechsler verbal intelligence scale (I) and the competency screening test (a sentence completion test of competence to stand trial). The group mean verbal I.Q. was 78. Verbal intelligence was not significantly associated with the clinical psychiatric evaluation finding of competence or incompetence. There was some suggestive evidence that verbal intelligence might be related to competency screening test scores for this subject population.

Seventeen patients were concordantly classified and only four discordantly classified by the clinical psychiatric evaluation and the competency screening test; both yielded significantly similar results. The competency screening test tended to classify more patients as incompetent (i.e., gave more positives), than did the clinical psychiatric evaluation. This greater inclusiveness was an important feature in a test designed to act as a screening instrument prior to more thorough clinical evaluation.

The competency screening test seemed to perform well as an initial screening procedure when validated against the more comprehensive clinical psychiatric evaluation. These results were consistent with the test's original experimental validation.

The present study extended the use of the competency screening test to an unselected female population in a large urban forensic psychiatric evaluation center where the mean verbal intelligence level was below average.

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Panic Disorder: Overview

JOEL H. KAPLAN, M.D.

Introduction

Panic disorder is a new diagnostic classification that will be included in DSM III. The name was evolved by me during work with Dr. Donald Klein at the Phobia Program at Long Island Jewish-Hillside Medical Center. The disorder represents a basic malfunctioning of the autonomic nervous system that is triggered centrally through the limbic system. It is a total body reaction that has both physical and psychological components. The hallmark of the disorder is a spontaneous panic attack that may produce symptoms of any or all systems innervated by the autonomic nervous system. It subsequently leads to the feeling of impending doom and terror. Table I describes symptoms of an acute panic attack.

In the early 1960's, work done by Dr. D. Klein and Dr. M. Roth in England led to the formulation of a phobic-anxious depersonalized syndrome characterized by phobia, anxiety and feelings of depersonalization and derealization (1, 2). At Hillside Hospital Dr. Klein, using the then new drug, Imipramine HCL, found that there was a subclass of inpatients who were neither psychotic nor severely depressed but who began to feel better while being treated with Imipramine (1, 3). The English found the same response, that is a blocking of the panic attacks with the use of MAO inhibitors (4). Stopping the panic attack was only one step in the total treatment of these patients. The majority of patients, following the onset of panic attacks, developed anticipatory and generalized anxiety. In a learning paradigm, they then developed phobias as a conditioned response. At its worse, the patient would have either severe agoraphobia or a mixed phobic picture including claustrophobia. The early work appeared to implicate severe early separation anxiety as a possible etiologic factor, but present evidence does not support this contention.

Present Outlook

Panic disorder may strike at any time of life for the first time. It is a condition that has been found in both males and females, children and geriatric patients. It is a chronic disorder that may stop and start throughout the patient's lifetime. The oldest patient that I treated was an 87-year-old woman who suffered with the disorder for 67 years before responding to a tricyclic drug. It has been found that all the tricyclics and MAO inhibitors can stop the panic attacks, while the phenothiazines actually worsen the clinical picture in a nonpsychotic patient. Benzodiazipines help the anticipatory anxiety but do not block the panic attacks. Panic disorder cuts across all diagnostic entities and is found in various personality types, including people who have not had any psychological difficulties prior to the onset of their first attack. The typical patient has multiple phobias, but panic disorder has also been found in obsessive-compulsive neurosis, manic-depressive illness, and even in schizophrenia. There are also patients who exhibit no secondary elaboration of symptoms, but instead, have symptoms of irritable colon, cardiac neurosis, or globus hystericus. In children, the disorder is mainly manifested as a school phobia (5). There is also another interesting class of patients who are addicts (6). They have become addicted to either alcohol, barbiturates, or other sedative hypnotics, in an effort to allay their severe anxiety and panic.

Treatment

The treatment of choice is with tricyclics or MAO inhibitors and supportive psychotherapy or behavioral therapy (7). In terms of drug treatment, panic disorder patients show a tremendous variability and response. Some patients may respond to a total of 1–10 milligrams per day while other patients may require up to 500 milligrams per day in order to stop the panic attack. Based on the latest research regarding tricyclic blood levels in depressed patients, one would anticipate that this wide range is indicative of different blood levels. In beginning treatment, the patient is asked to take 25 milligrams at bedtime (10 milligrams if they have a history of being sensitive to small amounts of neuroleptics) and report the following day as to how they are feeling. Doses may have to be adjusted on a daily basis until the patient reaches the point where there are no further attacks. Patient will then require continuing drug therapy for at least an additional six months, but many

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From the Department of Psychiatry, Mount Sinai Services, City Hospital Center at Elmhurst, Elmhurst, N.Y. 11373.

TABLE I
Acute Panic Inventory

1. Feeling faint
2. Fear of dying
3. Impending doom
4. Palpitations
5. Difficulty in breathing or rapid breathing
6. Frequent urgency to urinate
7. Frequent urgency to defecate
8. Dizziness
9. Confusion
10. Things and people are unreal
11. Feeling detached from part or all of body
12. Difficulty in speaking
13. Sweating
14. Difficulty in concentrating
15. Difficulty in doing a job
16. Twitching (limbs, grimacing)
17. Vomiting or nausea

patients require the medication for one to five years. In relation to the nondrug therapy, the therapy is designed to help the patient conquer the secondary elaboration of symptoms, whether they be phobias or obsessive-compulsive symptoms. One note of caution: Not all phobias or obsessive patients have panic disorder and medication only works better than placebo in patients who have a history of spontaneous panic attacks.

Etiology

At the present time, there is no known etiology. Based on work that has been carried out in the past decade in neuroendocrinology, I strongly suspect that we are dealing with a disorder of the hypothalamus and limbic system. My present theory is that thyroid releasing hormone, acting centrally, triggers the autonomic nervous system response.

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Diagnostic Significance of Antinuclear Antibodies in Pleural Effusion

MANOON LEECHAWENGWONG, M.D., HERBERT W. BERGER, M.D., AND MUTHIAH SUKUMARAN, M.D.

Abstract

The incidence of pleural fluid antinuclear antibodies (ANA) was examined in 100 consecutive patients—six with spontaneous systemic lupus erythematosus (SLE), one with procainamide-induced SLE, one with rheumatoid arthritis, and 92 with other conditions. ANA was found in the pleural fluid of all seven patients with spontaneous and drug-induced SLE, and was not found in the other patients. We conclude that the presence of ANA in pleural fluid is the most sensitive and may be the selective laboratory test for detection of pleural effusion caused by spontaneous and drug-induced SLE. The presence of pleural fluid ANA and low pleural fluid complement C3 suggests that an immune complex has formed locally and contributed to the occurrence of pleural inflammation and effusion in these disorders.

Introduction

Antinuclear antibodies (ANA) have been detected both in serum and in other body fluids (1). Although reported in pleural effusion caused by systemic lupus erythematosus (SLE), the specificity and incidence of pleural fluid ANA has not been carefully documented (2). In this report, we evaluate for the first time the diagnostic significance and selectivity of pleural fluid ANA in a study of 100 patients, including seven with spontaneous or drug-induced SLE.

Materials and Methods

A series of 100 consecutive patients with pleural effusions referred to the pulmonary disease service of The City Hospital Center at Elmhurst between April 1977 and November 1978 comprised the study population. All pleural fluids and some specimens of blood were centrifuged and the fluids stored at −20°C until tested.

Patients with diagnosed and suspected systemic lupus erythematosus (SLE) were classified according to the preliminary criteria for SLE as recommended by the American Rheumatism Association (3). Those diagnosed as having SLE fulfilled four of the 14 criteria, while patients diagnosed as having suspected SLE fulfilled two or three criteria. The patient with rheumatoid arthritis met criteria for classical and definite rheumatoid arthritis as defined by the American Rheumatism Association (4). The diagnoses of malignancy, parapneumonic effusion, empyema, tuberculosis, congestive heart failure, hepatic cirrhosis, pulmonary infarction, uremic pleurisy, and pancreatitis were made from commonly accepted clinical, pathologic, biochemical, bacteriologic, and radionuclide criteria. In 12 patients, the diagnoses were still undetermined after complete evaluation but no findings suggested systemic rheumatic disorders.

Antinuclear antibodies were determined by indirect immunofluorescent methods using the CSI Immunopath Fluoro-Kit for Lupus (ANA). Frozen rat liver served as substrate. The conjugate was fluorescein-labeled rabbit anti-human globulin. The ANA test is used in our hospital as a screening test in conjunction with the lupus erythematosus (LE) cell test. An ANA test is considered positive when a 1:10 dilution of serum or pleural fluid gives positive nuclear fluorescent staining of any of the four staining patterns. Results were read with a fluorescence microscope (Leitz) equipped with mercury vapor lamp (HBO 200) with a BG 12 exciter filter, oil immersion darkfield condenser, K510 barrier filter, and 10× dry and 54× oil objectives.

Results

The clinical features of the seven patients with spontaneous and procainamide-induced SLE are shown in Table I. Pleuritic chest pain and pleural effusion were initial manifestations in all seven patients. Two patients failed to meet the full ARA criteria for SLE; however, we believe they had sufficient clinical features to be

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From the Pulmonary Section, Department of Medicine, Mount Sinai Services, The City Hospital Center at Elmhurst, Elmhurst, N. Y., and from Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Dr. Herbert W. Berger, Mount Sinai Services, City Hospital Center at Elmhurst, 79-01 Broadway, Elmhurst, N. Y. 11373.

TABLE I
Clinical Features of Seven Patients with Spontaneous and Drug-induced SLE

Sex	Age	Clinical Features	Comments
F	21	Left pleurisy and pleural effusion, fever, arthritis, facial erythema, LE cells, positive serum ANA, low serum and pleural fluid complement C3 Kidney biopsy—no abnormality	Diagnosed SLE Satisfies 4 ARA criteria
F	53	Right pleurisy, bilateral pleural effusions, pericardial effusion, fever, arthritis, subcutaneous nodule, anemia, leukopenia, LE cells, positive serum ANA, low serum and pleural fluid complement C3	Diagnosed SLE Satisfies 4 ARA criteria
F	34	Left pleurisy, bilateral pleural effusions, pericardial effusion, fever, arthritis, photosensitivity, oral ulcers, facial erythema, thrombocytopenia, positive serum ANA, negative LE cells, low serum and pleural fluid complement C3	Diagnosed SLE Satisfies 6 ARA criteria
M	35	Left pleurisy and pleural effusion, pericardial effusion, fever, arthritis, right C.V.A., hemolytic anemia, thrombocytopenia, positive serum ANA, negative LE cells, low pleural fluid complement C3	Diagnosed SLE Satisfies 4 ARA criteria
M	46	Left pleurisy and pleural effusion, pericarditis, fever, arthritis, hematuria, LE cells, positive serum ANA, low pleural fluid complement C3 Kidney biopsy—mild nonspecific changes	Suspected SLE Satisfies 3 ARA criteria
F	70	Left pleurisy and pleural effusion, pericardial effusion, fever, arthritis, positive serum ANA, negative LE cells, low serum and pleural fluid complement C3	Suspected SLE Satisfies 2 ARA criteria
M	66	Right pleurisy, bilateral pleural effusions, pericardial effusion, fever, arthritis, LE cells, positive serum ANA, low pleural fluid complement C3 On procainamide for 6 months	Procainamide-induced SLE

TABLE II
Incidence of Positive ANA Tests in Pleural Effusions

Condition	No. Positive/Total
Malignant pleural effusion	
Primary lung carcinoma	0/19
Metastatic lung carcinoma	0/9
Mesothelioma	0/1
Multiple myeloma	0/1
Lymphoma	0/4
Infection	
Parapneumonic effusion	0/7
Empyema	0/8
Tuberculosis	0/6
Congestive heart failure	0/12
Cirrhosis of the liver	0/3
Connective tissue disease	
SLE	4/4
Suspected SLE	2/2
Procainamide-induced SLE	1/1
Rheumatoid arthritis	0/1
Miscellaneous	
Pulmonary infarction	0/7
Uremic pleurisy	0/2
Pancreatitis	0/1
Indeterminate	0/12
TOTAL	7/100

included in the broad definition of suspected SLE. No patients had significant renal abnormalities. The patient with rheumatoid arthritis for seven years had shortness of breath and bilateral pleural effusions. She had positive serum rheumatoid factor and ANA but no LE cells. Her pleural fluid showed sugar 0 mg/100 ml, characteristic rheumatoid arthritis (RA) cells, and low complement C3 (5).

The incidence of positive pleural fluid ANA determinations in different disease entities studied is summarized in Table II. The incidence of positive serum ANA in our study is not known since serum ANA was determined only in patients suspected to have connective tissue diseases.

Discussion

The indirect immunofluorescent ANA (IF-ANA) test is a useful screening procedure (6). However, positive serum ANA tests have been reported in many conditions in addition to SLE, such as other connective tissue diseases, drug reactions, chronic active hepatitis, myasthenia gravis, and even in completely asymptomatic individuals. The mere presence of serum ANA therefore has little specific diagnostic significance. This contrasts with our finding of ANA in pleural fluid where ANA was present in the seven patients with spontaneous and procainamide-induced SLE and was not found in 93 patients with other diagnoses. One patient with characteristic rheumatoid pleural effusion who had ANA in her serum did not have ANA in her pleural fluid. Since we did not determine serum ANA in all patients, it is likely that more patients with diagnoses other than SLE may have had ANA in their blood but no ANA in their pleural fluid. Our findings are in line with the experience of Chandrasekhar et al who studied in vivo immunofluorescent staining of antinuclear antibody deposition in the pleura of 36 patients with pleural effusions of varied etiology (7). Specific nuclear fluorescence was only detectable in the three patients with procainamide-induced SLE. Four patients with pleural effusion caused by other diseases who had ANA in their blood did not have in vivo antinuclear staining in their pleural tissue. This finding of positive serum ANA but negative pleural fluid ANA or ANA deposition in the pleura in diseases other than spontaneous or drug-induced SLE makes it unlikely that the presence of pleural fluid ANA is due to passive diffusion of ANA from blood into pleural fluid. Hunder et al detected antinuclear factor in pleural fluid from all five patients with SLE, but no antinuclear factor in four patients with rheumatoid arthritis (8). We conclude that the presence of ANA in pleural fluid may be selective for spontaneous and drug-induced SLE; however, this needs confirmation in a larger population including more patients with other connective tissue diseases. Both the titer and pattern of ANA test should be reported in future studies.

Pleuritis and pleural effusion are found in half the patients with spontaneous and drug-induced SLE, a higher incidence than in other connective tissue disorders (9). Pleuritis with or without pleural effusion may be the initial manifestation of SLE as was seen in our seven patients (10). Pleural fluid in spontaneous and drug-induced SLE is usually an exudate with low cell count and polymorphonuclear percentage, normal glucose concentration, and with no characteristic findings except the occasional presence of LE cells (11). Our study suggests that ANA in pleural fluid is the most sensitive and may be the selective laboratory test for detection of pleural effusion due to spontaneous and drug-induced SLE. It may be clinically helpful in differentiating rheumatoid arthritis with pleural effusion from SLE with pleural effusion. The presence of low complement and ANA in pleural fluid in spontaneous and drug-induced SLE and in vivo fixation of antinuclear antibodies in the pleura of patients with drug-induced SLE suggest that an immune complex has formed and contributed to the occurrence of pleural inflammation and effusion in these disorders.

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The Use of Lithium in Cyclical Behavior Disorders of Adolescence: A Case Report

PAVLOS KYMISSIS, M.D., D.M.S., BONNIE PADRUSCH, M.S., AND DAVID SCHULMAN, M.D.

Introduction

Although it was in the middle of the nineteenth century that Falret and Baillarger first described a mental illness with recurring attacks of mania and melancholia, it was not until late in the nineteenth century that Kraepelin firmly established the disorder as a "uniform disease entity" distinct from schizophrenia (1). His description of manic-depressive illness is accepted as valid through today. However, although the presence of a schizophrenic disorder is now accepted as occurring during childhood and adolescence, the emergence of manic-depressive disease during these stages remains in dispute.

Rather than become involved in a dispute over diagnostic considerations at this time, it is our intention to focus on the issue of behavioral symptoms in adolescence as representing possible manifestations of affective disorder and the use of lithium in the treatment and prophylaxses of such conditions.

Easson, in his work *The Severely Disturbed Adolescent,* stated his belief that manic-depressive symptoms may occur more frequently than thought in adolescence, but that the affective symptoms are more likely to be expressed in physical activity or in somatic symptomatology. Just as we speak of depressive equivalents, there may be manic equivalents or, in general, affective equivalents, which may be expressed in behavioral patterns that will be identified in time. Behavioral patterns during childhood and adolescence need to be examined against the background of the developmental stage during which they occur, and in the light of genetic, familial and environmental history. Some authors suggest that because of the emotional upheaval that occurs with the various developmental stages, affective symptoms can be misread as representing exacerbations of the normal stages (3). Confusion in diagnosis results because the mood swings in adolescence are of shorter duration than those that occur in the typical manic-depressive disorders of adulthood.

Various researchers have listed the criteria necessary for the establishment of the existence of manic-depressive states in younger patients (4, 5). The use of lithium in various affective disorders of both children and adults has received considerable attention (6–9).

An in-depth chronological study of a few patients in such diagnostic categories as mentioned above has been made by the authors on various occasions and it has suggested that affective equivalents may become manifest in a cyclical pattern of alternating symptoms, characterized by silly, excited, hyperactive, irritable, paranoid, withdrawn, angry, or explosive behavior.

Case Report

One such case that dramatically illustrated the effectiveness of lithium in containing a cyclical disorder of psychotic proportions came to our attention when, in preparation for the Division's male adolescent ward's weekly case presentation, a day by day behavioral assessment of the patient's behavior revealed a peaking in episodic psychotic behavior on or about the 23rd day of each month during the course of the patient's hospitalization.

This was the fourth psychiatric hospitalization (second in our facility) of a 16-year-old adolescent male who had spent eight years of his life in various residences and hospitals. He was admitted from a residential treatment center, as his behavior there had become increasingly depressed, paranoid, bizarre, disruptive, and assaultive.

As the middle child, born between two sisters, he was described as being a placid baby until he began crawling, and from then on as an increasingly hyperactive and accident prone boy throughout early childhood. He was diagnosed as hyperactive at age seven, and first placed in residence at age eight. More recent diagnoses have been of schizophrenia often with depressive and explosive features. Behavioral descriptions appended to the diagnoses in summaries were depression, marked hyperactiv-

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From the Division of Child and Adolescent Psychiatry, Department of Psychiatry, Mount Sinai Services—City Hospital Center at Elmhurst, Elmhurst, N.Y. 11373.

ity, lability and inappropriateness of affect and behavior. During his first hospitalization in this setting at age 14, he was described as hyperactive, loud, playful and provocative, and alternately depressed. He had rambling speech, a short attention span, and, at times, a flight of ideas. Family history as reported by the patient's mother was negative on her side, but positive for paternal pathology. Various members of the father's family were described by her as being schizoid personalities, or as depressive. Some had a history of alcohol abuse, and two had been in institutions for the criminally insane.

Over the course of a seven-month period of hospitalization, the patient manifested three acute psychotic episodes on or about the 23rd day of each of the first three months of his stay. Traditional medication approaches of phenothiazines and psychotherapy proved inadequate to contain these decompensations as they had failed to provide adequate, sustaining help in the past.

Since cyclic behavioral changes were considered to be affective equivalents, his difficulties were viewed as representing a manic-depressive disorder and it was decided to attempt a course of treatment with lithium. Lithium was initiated during the fourth month of hospitalization, on the 19th of the month. Behavior became rapidly quieter and more contained and no further acute episodes developed over the remaining four months of hospitalization.

The lithium blood level rose to 1.2 meq/L on 1500 mg/day, but it was necessary to use thorazine and stelazine as well in order to maintain control. Medications had to be decreased one week later as the patient began to manifest early toxic symptoms (nausea, anorexia, weight loss, drowsiness) at the 1.2 meq/L level. Lithium alone was reinstated at the end of the fifth month of hospitalization at 900 mg and then raised to 1500 mg/day, where it has remained with a fairly well-maintained blood level of 0.9 meq/L. Neuroleptics were not employed again. Since the onset of lithium therapy, his behavior has markedly improved. He is more stable, cooperative and manageable, with considerably less lability, although the basic difficulty in relating to other people continued.

Practical Implications

The successful use of lithium as a stabilizer of a cyclic behavioral disorder of psychotic proportions in an adolescent boy has been detailed in the preceding report. In our opinion consideration of the following points could prove of value.

1. Affective equivalents of a behavioral disorder could represent early manifestations of manic-depressive illness. It is important to rule out other possibilities as bearing etiologic significance, such as central nervous system (CNS) disease, and endocrinological or metabolic disorders.
2. The cyclic nature of the behavioral disorder could be determined not just by a cross-sectional evaluation through the mental status examinations, but by a carefully detailed day by day chronicle of the patient's longitudinal history.
3. Such cyclic or periodic psychopathologic patterns that are often resistant to traditional approaches with phenothiazines, or other antipsychotic agents, may respond to lithium.
4. Further, carefully designed controlled research studies of adolescents with periodic psychotic behavioral disorders of a cyclic nature are needed to determine the use of lithium as a treatment modality.
5. The behavioral manifestations described in this case as potentially representing the affective equivalents of a mood disorder may, in fact, prove to be related to other underlying biologic, endocrinologic, metabolic or CNS pathology.
6. Lithium may prove to be an effective treatment modality of cyclic or periodic psychotic disorder in adolescents unrelated to manic-depressive disease.

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Sclerema Neonatorum Complicated by Radial Nerve Palsy Following Nontraumatic Delivery

BERT A. COPPOTELLI, M.D., JOHN D. LONSDALE, JR. M.D. AND ELAINE KASS, M.D.

Introduction

Sclerema neonatorum is an infrequent condition of uncertain etiology. Developmental alterations in the biochemical constituents of subcutaneous fat have been hypothesized. Alternately, an intrapartum-acquired etiology associated with trauma represents the prevailing opinion since sclerema neonatorum is most often seen in association with traumatic delivery and/or peripheral circulatory impairment associated with vasoconstriction (1).

We have had the unusual experience of observing an otherwise normal infant spontaneously delivered vaginally who, nevertheless, was detected at eight hours of age to have unilateral radial nerve palsy associated with sclerema.

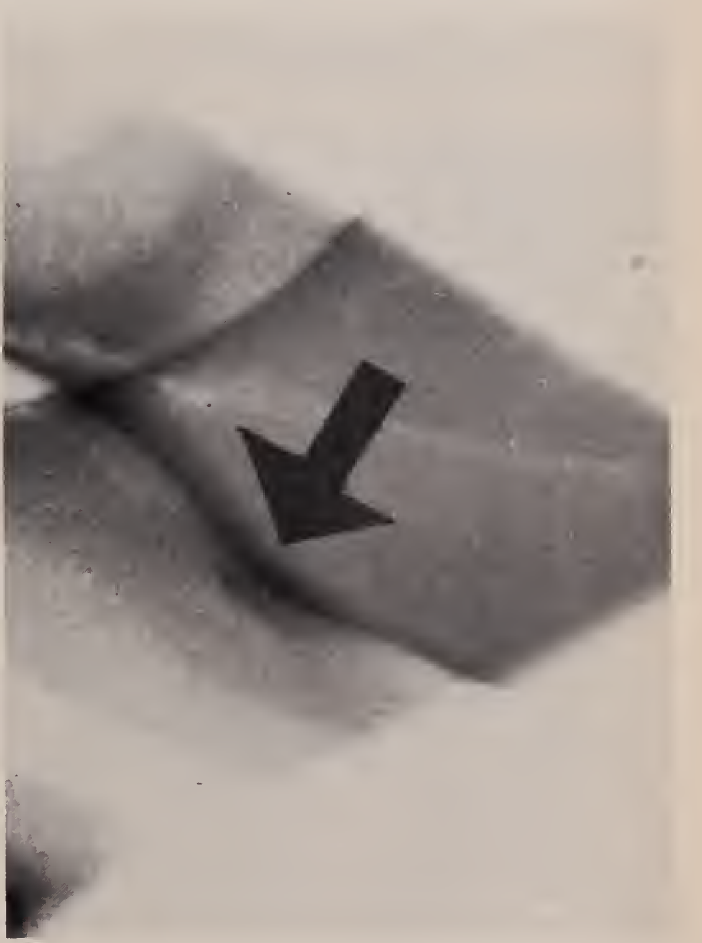
Case Report

Clinical Picture: A black male, weighing 3800 grams, was born at full term to a 24-year-old gravida one, para one mother whose pregnancy was uneventful. The total duration of labor was 29.5 hours. The delivery was not assisted by forceps. An episiotomy was not necessary as the birth proceeded without problems. The boy's initial Apgar score was eight at one minute and nine at five minutes.

It was immediately observed that the infant had a flexed drop of his right wrist. It was not possible to assess any alterations in sensation; there was no evidence of muscle atrophy. Klumpke's palsy due to traction on the lower nerve roots of the brachial plexus was discounted as the etiology in the absence of any intrapartum trauma. The baby was otherwise normal on detailed neurologic examination; however, closer examination of the soft tissues of the right upper arm revealed a dimple-like depression measuring 1.5 in diameter (Fig. 1). This was at the area of insertion of the deltoid muscle.

About 24 hours later, a bluish discoloration in the area of the dimple that had a nodular sensation on palpation was observed. Over the next few days, similar nodules developed on the right axilla and pectoral areas.

Electromyography: Detailed study of both upper extremities conducted on the fourth and eighth day of life revealed isolated, complete peripheral right radial nerve palsy, however by the 22nd day, there was revealed



Above reverse negative x-ray of right upper extremity shows dimpling in the region of the deltoid insertion which compromised radial nerve distribution.

From the Department of Pediatrics, Mount Sinai Services—City Hospital Center at Elmhurst, Elmhurst, N.Y. 11373.

beginning improvement. The repeat electromyogram (EMG) report on the eighth day stated that there was " . . . persistent absence of motor units in forearm extensor muscles with development of fibrillation and positive waves in large numbers." On the 22nd day the baby was improved EMG-wise. He had a few motor units in the forearm extensor group muscle that were totally denervated in the previous study.

Tissue Biopsy: A biopsy was performed on the ninth day and was taken from the axillary nodular material. Although the overlying skin was normal, the subcutaneous tissue revealed " . . . numerous foci of fat necrosis with foreign body giant cells, lymphocytes, plasma cells and histiocytes. There are many needle-shaped empty clefts in radial arrangement of the fat cells." The diagnosis rendered was sclerema neonatorum.

Clinical Course: The infant's general condition was excellent. The nodular areas described above began to involute slowly leaving no dimple-like depressions or firm nodules in the ensuing three weeks. An extensor splint was applied to the right wrist; progressive physiotherapy was continued for three weeks. On follow-up visit at that time, movement in the affected area was noted to have improved. Subsequently, the child was lost for follow up.

Discussion

Sclerema neonatorum is generally an accompaniment of either some general disorder (prematurity, shock, acidosis, dehydration, asphyxia, etc.) or the consequence of a traumatic delivery. When associated with a generalized metabolic aberration, the condition is generally described as acute generalized sclerema or acute diffuse hardening of skin. This type is usually found in the newborn period secondary to shock, but also appears at times later in infancy after acute dehydration. It is usually associated with a poor clinical condition such as cyanosis, respiratory difficulties, etc. (5). The form of sclerema neonatorum associated with intrapartum trauma is also called benign circumscribed sclerema. This type appears in the first week of life and trauma is usually the causative factor. It generally undergoes resolution over a few months period, at times by cyst-like formation and calcification. Giant cell formation and lymphocytic infiltration is seen in the lesion (5).

The infant we describe has certain chemical and histologic features consistent with two important exceptions (2). First, there is the absence of intrapartum trauma and therefore the etiology is regarded as idiopathic. Second, and also of considerable interest, this is an infant whose local area of involvement was anatomically associated with peripheral pure radial nerve palsy and with no other neurological defect.

Isolated radial nerve palsies in neonates not due to Klumpke's traction of the cervical spinal cord are rare (6). We believe that the coincidence of a scleremic nodule compressing the radial nerve is the appropriate explanation for our unusual baby.

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Septic Pulmonary Infarction: Clinical and Radiographic Manifestations in 11 Patients

CLEMENT OSEI, M.D., HERBERT W. BERGER, M.D., AND PETER NICHOLAS, M.D.

Abstract

The clinical and radiographic features in 11 patients with septic pulmonary infarction (SPI) are presented. Six patients were heroin addicts and two were on maintenance hemodialysis. Staphylococcus aureus was cultured from the blood in eight patients and other single or multiple organisms in three. Of note were the occurrence of chest pain in ten patients and white blood cell counts below 10,000 per cu mm in six patients. Despite a prolonged duration of symptoms prior to hospitalization, some patients did not appear toxic on admission. The most common radiographic abnormalities were bilateral, poorly circumscribed 1-3 cm nodules most frequently one to ten in number found in every patient, accompanied by thin-walled, occasionally fluid-filled cavities in nine. Areas of patchy consolidation occurred in three patients and pleural effusion in six. In four patients, progressive radiographic changes were noted after antibiotic therapy was started. Until results of blood cultures are available, we generally recommend intravenous oxacillin in drug addicts or patients on maintenance hemodialysis with suspected SPI. Patients who appear toxic or have significant hypotension should be given an aminoglycoside in addition to oxacillin or clindamycin. Antibiotic treatment was continued for four to nine weeks. Closed tube thoracostomy was performed when empyema was recognized. Fever resolved slowly over two to three weeks in most patients. Three patients died, all due to noninfectious complications.

Introduction

The incidence of septicemia reported in narcotic addicts and patients on maintenance hemodialysis has recently increased (1–3). Septic pulmonary infarction (SPI) is a well-recognized complication resulting from septic thrombophlebitis or right-sided bacterial endocarditis in patients with these medical problems (4, 5).

The chest roentgenograph is crucial in leading to early diagnosis and treatment of SPI. Hussey and Katz in 1945 reviewed eight cases (4). Since the reports of Fred and Harle in 1969, and Jaffe and Koschmann in 1970, SPI has received little attention in the literature (6, 7). In this article, we review the clinical and radiographic features of septic pulmonary infarction in 11 patients and compare the findings with those previously described.

Materials and Methods

The 11 patients in this report were evaluated by the Pulmonary Disease Service of the Mount Sinai Services-City Hospital Center at Elmhurst between 1966 and 1977 and selected from a review of our consultation records. All 11 patients had at least two positive blood cultures, clinical evidence of generalized infection, and chest radiographic abnormalities. A diagnosis of empyema was made when pleural fluid appeared purulent or cloudy due to increased white blood cells; a positive pleural fluid culture was not always present since most patients were already on antibiotic therapy when thoracentesis was performed. A diagnosis of endocarditis was made in one patient at autopsy and from clinical evidence of changing murmurs in three patients.

Results

Table I shows age, sex, foci of infection, and duration of symptoms prior to hospitalization. Symptoms are listed in Table II. White blood cell (WBC) counts on admission ranged from 6,100 to 17,500 per cu mm. Six patients had WBC counts less than 10,000 per cu mm. Ten patients were anemic, six with hemoglobin levels less than 10 gm per 100 ml on admission to the hospital. Table III shows organisms cultured from the blood and other sources, complications, antibiotics, and duration of therapy. Radiographic features are summarized in Table IV and illustrated in Figure 1.

From the Pulmonary and Infectious Disease Services, Department of Medicine, Mount Sinai Services-City Hospital Center at Elmhurst, Elmhurst, N. Y., and Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Herbert W. Berger, M.D., Mount Sinai Services-City Hospital Center at Elmhurst, 79-01 Broadway, Elmhurst, N. Y. 11373.

Discussion

SPI results when an infected thrombus from right-sided endocarditis, particularly tricuspid valve, or septic thrombophlebitis lodges in the pulmonary circulation causing infarction and suppuration (4). This now occurs most frequently in heroin addicts and patients on maintenance hemodialysis, as seen in this study in six and two patients respectively. Other initial foci of infection reported here and in the literature include peritonsillar abscess, subcutaneous abscess, cellulitis, septic abortion, urinary tract infection, osteomyelitis, and suppurative arthritis (5). Attempts have been made to differentiate SPI from metastatic pulmonary abscesses resulting from emboli consisting only of bacteria (4, 8). Unless pulmonary angiography is performed, this differentiation is extremely difficult. We avoided the distinction since similar initial treatment with antibiotics is indicated in both groups.

In our 11 patients radiographic manifestations of septic pulmonary infarction were frequently the earliest sign of serious illness, particularly since some patients did not appear toxic. Addicts, in particular, often have misleading complaints late in the course of infection. Six patients had been symptomatic for more than seven days and one for six weeks prior to hospitalization. Noteworthy is that the occurrence of chest pain in ten patients and empyema in five is significantly more frequent than previously

TABLE I

Clinical Features in 11 Patients with SPI

Patient no.	Age	Sex	Foci of infection	Duration of symptoms prior to hospitalization (days)
1	16	F	Peritonsillar abscess	21
2	22	F	Heroin use	8
3	16	M	Cellulitis of face	2
4	18	M	Heroin use	4
5	43	M	Dialysis, heroin use	2
6	26	M	Heroin use, infected ulcer foot	2
7	23	M	Heroin use	20
8	55	M	Dialysis, abscess forearm	5
9	23	F	Heroin use	42
10	64	M	Urinary tract infection	28
11	26	F	Septic abortion	28

TABLE II

Symptoms in 11 Patients with SPI

Symptoms	No. of Patients
Fever (101° – 105° F)	11
Chest Pain	10
Cough	10
Chills	6
Weakness	3
Myalgia	2
Dyspnea	2
Hemoptysis	1

TABLE IV

Radiographic Features in 11 Patients with SPI

		No. of patients
Nodules 1–3 cm	<5	4
	5–10	5
	>10	2
diffuse nodules 2–4 mm		3
cavities (fluid)		9 (3)
predominant localization of nodules	lower lobes	9
	upper lobes	2
patchy consolidation		3
pleural effusion		6
rapid progression		4

TABLE III

Cultures, Therapy, and Complications in 11 Patients with SPI

Patient	Blood cultures	Other cultures	Complications	Antibiotics	Duration of therapy (weeks)
1	fusobacterium necrophorum	—	empyema	penicillin, clindamycin	5
2	s. aureus	—	empyema	oxacillin	6
3	s. aureus	s. aureus - face abscess	—	oxacillin, cephalothin, lincomycin	6
4	s. aureus	—	—	oxacillin, penicillin	7
5	s. aureus	—	—	cephalothin, vancomycin	4
6	anaerobic streptococcus, bacteroides sp.	bacteroides sp. - empyema	empyema, endocarditis	clindamycin	7
7	s. aureus	s. aureus - urine	endocarditis, empyema	oxacillin	6
8	s. aureus	s. aureus - forearm	—	oxacillin	expired acute MI,* massive GI** bleeding
9	s. aureus	—	empyema, endocarditis	cephalothin, clindamycin	9
10	enterococcus	enterococcus - urine	endocarditis	penicillin, streptomycin	expired pulmonary edema
11	s. aureus	—	—	methicillin	expired GI bleeding

* MI - acute myocardial infarction

** GI- gastrointestinal

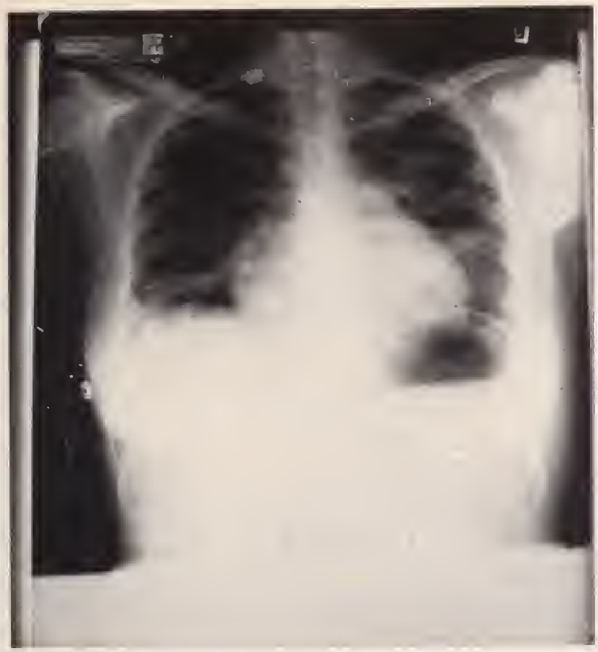

Fig. 1. Chest x-ray showing nodules, cavitation, and right pleural effusion.

reported (3, 9). Every patient had fever and ten had nonproductive cough. The frequency of empyema and chest pain in SPI is due to the peripheral nature of lesions, with pleural involvement by the suppurative process. Occurrence of chest pain in any addict with fever requires prime consideration of the diagnosis of SPI and careful chest radiographic studies and blood cultures. A diagnosis of SPI in turn requires a search for right-sided endocarditis and areas of suppurative thrombophlebitis. A potentially misleading finding was a normal initial white blood cell count in more than half of our patients.

Staphylococcus aureus, isolated from the blood in eight patients, was the most common causative organism, as seen in previous series (1, 3, 10). Sputum cultures failed to reveal S. aureus in any patients; this indicates that one must not rely on sputum cultures in diagnosis of SPI. Tuazon and associates found a 300 percent increase in the carrier rate of S. aureus among parenteral drug addicts as compared to the general population, a fact which may in part explain the high prevalence of this organism in addicts with sepsis (3). A subcutaneous abscess may or may not be found. Other organisms cultured included Fusobacterium necrophorum, enterococcus, bacteroides sp., and anaerobic streptococcus. One patient grew two different organisms in the blood.

The radiographic abnormalities in SPI must be differentiated from suppurative bacterial pneumonia and metastatic pulmonary neoplasm (4, 7, 9). The most common changes seen in the patients were bilateral, 1-3 cm poorly circumscribed nodules, most frequently one to ten in number, and thin-walled cavities which occasionally contained fluid. All 11 patients had nodules, nine had cavitation, and three had fluid-containing cavities. Even though there was lower lobe predilection of nodules, those in the mid and upper lung fields were more likely to cavitate. Patchy areas of consolidation were seen in three patients, and 2-4 mm nodular diffuse infiltrations in three patients. Unilateral or less frequently bilateral pleural effusions were common, with documented empyema in five patients. Rapid progression in size and number of nodules, development or enlargement of cavitation, and appearance or increase of pleural effusion occurred frequently, even after effective antibiotic therapy was instituted. In several patients the initial radiographic changes were subtle and recognized only when compared with follow-up films. Resolution of radiographic lesions was slow and required three to seven weeks. Residual pulmonary infiltrations and/or pleural thickening were usually present following treatment.

We generally recommend intravenous oxacillin in drug addicts and patients on maintenance hemodialysis with suspected SPI. Patients who appear toxic or have significant hypotension should receive oxacillin or clindamycin plus an aminoglycoside to provide coverage for possible aerobic gram negative bacilli and anaerobes. Other patients should receive therapy based upon the most likely organism as determined clinically and confirmed by cultures and sensitivity studies.

In spite of parenteral antibiotics, fever continued for two to three weeks in most patients and as long as four weeks in some patients, especially those with endocarditis. Continued embolization to the lungs may explain prolonged fever in those with endocarditis, but in others extensive lung involvement and occurrence of empyema were more likely causes. We found little evidence that drug allergy or superinfection led to prolonged fever, although they are considered important by Tuazon (3). Failure of the fever to resolve rapidly was not considered a reason to change antibiotics, provided the patient showed other clinical signs of improvement and sensitivity tests, including serum bactericidal levels, as well as susceptibility to the organism. In addition to antibiotics, five patients were treated with closed-tube thoracostomy for empyema drainage. The eight patients who survived were treated for four to nine weeks. None of these patients relapsed, had further major complications of their infection, or required surgery other than chest tube drainage for empyema. Death in three patients was caused by noninfectious medical problems including myocardial infarction, pulmonary edema, and gastrointestinal bleeding.

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Speed and Recovery of Anaerobes from Clinical Specimens: Evaluation of Two Methods

MOISES S. MALOWANY, M.D., FCAP, GEORGE MIKKELSEN, SM (ASCP) AND JONA ALLERHAND, M.D., FCAP

Introduction

It has been clearly established that anaerobic bacteria can cause serious infections in humans (1–4). Depending on methods used for isolation, different investigators have reported various recovery rates of anaerobes from clinical specimens. Using a combination of broth enrichment cultures streaked onto blood agar plates and incubated in GasPak jars, low recovery rates have been reported, whereas significantly higher rates were obtained with direct inoculation technics (5–8).

The aim of this study was to compare the relative abilities of thioglycollate for initial inoculation followed by subculture to blood agar plates incubated in gaspak jars (Th-GP) and roll streak methodologies to isolate anaerobes. This evaluation was performed on both known mixed cultures and on clinical specimens.

Materials and Methods

The following media were used in the study: Prereduced anaerobically sterilized (PRAS), supplemented brain heart infusion roll streak tubes (RS), chopped meat carbohydrates (CMC), and peptone yeast glucose (PYG). PRAS media were manufactured using the formulas in the VPI Manual (9). Conventional media used included fluid thioglycollate medium without dextrose, with resazurin indicator (Th), trypticase soy agar base with 5% sheep blood agar plates (BAP), phenylethyl alcohol agar with 5% sheep blood (PEA), and MacConkey agar.

The bacteria used in the laboratory-prepared mixed cultures were obtained from specimens received in this laboratory. The anaerobes were isolated and identified according to methods outlined in the VPI manual (9). The facultative bacteria were isolated and identified following the procedures in the ASM manual of clinical microbiology (10). Each anaerobic and facultative microorganism was inoculated into both a PRAS RS tube, and a BAP incubated in a GasPak jar to assure purity and adequate growth on these media.

Mixed cultures to simulate specimens from infections were prepared as outlined in Table I by pooling equal volumes of the microorganisms grown in broth cultures for 24 hours at 37° C. Each mixed culture consisted of one obligately anaerobic organism and one to four facultative anaerobes. The resulting 16 mixtures were inoculated onto PRAS RS tubes according to VPI procedures (9).

After 18-hours incubation, RS tubes were inspected under a dissecting microscope using 10× magnification, and each different colony subcultured onto two BAP; one was incubated aerobically and the other anaerobically in a GasPak jar. A methylene blue indicator was included in the jar and the catalyst was changed with each use. Comparison of the aerobic and anaerobic BAP was made to determine the recovery of obligate anaerobes.

A second set of 16 cultures was processed by inoculating thioglycollate broth. Only unoxygenated broths were used (as indicated by the resazurin). After 18-hours incubation at 37° C, subcultures were made to BAP and PEA and incubated in a GasPak jar. The next day, each colony type was streaked to two BAP that were further processed as previously described.

Clinical specimens selected for the study are listed in Table II. Swabs were sent in Amies Transport Media and aspirates were either sent in anaport bottles or brought to the laboratory in capped syringes.

Cultures were first processed by RS methodology as follows: a gram stain was made and examined immediately; then inoculations were made directly on PRAS RS tubes and CMC broth. RS tubes were processed as the laboratory-prepared cultures. Each colony isolated was also inoculated to a PRAS PYG broth. Those PYG broths containing obligate anaerobes were used for the inoculation of biochemicals and analysis by gas-liquid chromatography (GLC). The GLC used was the Dohrmann model anabac following procedures recommended in the VPI Manual (9).

A genus was determined based on the results of the

From the Department of Laboratories, Mount Sinai Services, City Hospital Center at Elmhurst, N.Y. and Mount Sinai School of Medicine, New York, N.Y. 11373.

TABLE I

Isolation of Anaerobes from Laboratory-Prepared Cultures

Anaerobe	Facultative	Th-GP method	RS method
B. fragilis*	E. coli	+	+
	E. coli, S. aureus	+	+
	E. coli, S. aureus, enterococcus	+	+
	E. coli, S. aureus, enterococcus, P. mirabilis	+	+
C. perfringens	E. coli	+	+
	E. coli, S. aureus	+	+
	E. coli, S. aureus, enterococcus	+	+
	E. coli, S. aureus, enterococcus, P. mirabilis	+	+
E. limosum	E. coli	−	+
	E. coli, S. aureus	−	+
	E. coli, S. aureus, enterococcus	−	+
	E. coli, S. aureus, enterococcus, P. mirabilis	−	+
P. anaerobius	E. coli	−	+
	E. coli, S. aureus	−	+
	E. coli, S. aureus, enterococcus	−	+
	E. coli, S. aureus, enterococcus, P. mirabilis	−	−

* Each culture consisted of a mixture of the indicated anaerobe plus up to four facultative bacteria.

+: Anaerobe was isolated from mixed culture

−: Anaerobe was not isolated from mixed culture

GLC and an analysis of gram stains of the PYG culture. After incubation of the biochemicals, the species was determined accordingly.

Simultaneously with culturing by RS procedures, specimens were processed by standard bacteriologic technics, including the inoculation of BAP, PEA, MacConkey, and thioglycollate and incubated aerobically. An examination of gram stains of the thioglycollate for typical morphotypes combined with the evaluation of aerobic growth on the plates was used to determine the presence of anaerobes. If anaerobes were suspected, a BAP and PEA were inoculated and incubated in a GasPak jar. These plates were further processed as described for the laboratory-prepared cultures. In general, anaerobes were identified to the genus level by gram stains of isolates growing only on anaerobic plates. Clostridium perfringens was identified further by the production of stormy fermentation in litmus milk and a double zone of hemolysis on BAP.

Results

The results of the laboratory-prepared mixed cultures are shown in Table I. This table was a compilation of three replicate tests of these cultures, the results of which were substantially identical. On RS tubes, Bacteroides fragilis, Clostridium perfringens, and Eubacterium limosum were isolated from all cultures containing up to four facultative bacteria. However, Peptostreptococcus anaerobius was isolated only from cultures containing Escherichia coli, Staphylococcus aureus, and an enterococcus, but not when Proteus mirabilis was added to the mixture.

Using the Th-GP procedures only B. fragilis and C. perfringens were isolated from cultures containing up to four facultative organisms. E. limosum and P. anaerobiu were not isolated from any laboratory-prepared mixe culture.

TABLE II

Sources and Results of Clinical Specimens

Source	No. Growth	Positive cultures	Cultures containing anaerobes	Total
Wound	23	212	52	235
Abscess	10	78	15	88
Peritoneal	46	78	18	124
Pleural	50	30	1	80
Other*	35	69	23	104
Total	164	467	109	631

* Includes knee, ear, sinus and transtracheal.

TABLE III

Comparison of the Number of Anaerobes Isolated from Clinical Specimens

Method	RS*	Th-GP**
Number of specimens	109	38
Number of isolates	144	43
Specimens with one anaerobe	66	33
Specimens with multiple anaerobes	43	5

* Roll Streak

** Thioglycollate-GasPak

The results of the clinical specimens are shown i Table II. A total of 631 specimens were processed; 16 specimens did not grow any organism. Of the 467 specimens containing bacteria, 385 did not grow anaerobes. A least one species of obligate anaerobe was isolated fro the remaining 109 specimens.

Table III shows the difference in the number of anaerobes isolated by the two procedures. By using RS methodology, 144 anaerobes were recovered from 109 specimens, whereas only 43 anaerobes from 38 specimens wer isolated using the Th-GP procedure. A total of 117 anaerobes were isolated by RS methodology that were no recovered by the Th-GP procedure. More than one species of anaerobe were isolated from 43 specimens wit the RS method, but from only five specimens for the Th-GP method.

Table IV lists the kinds of anaerobes recovered. Usin RS methodology, various species of bacteroides accou for the greatest number of isolates, followed by th anaerobic gram-positive cocci. Twenty isolates of bacteroides and ten isolates of anaerobic cocci could not b further identified. Various species of Clostridia were ne in frequency, followed by occasional isolates of oth genera.

Bacteroides species were the organisms most ofte isolated by Th-GP procedures. Next in frequency we various species of clostridia followed by anaerobic gra positive cocci and nonsporeforming gram-positive rods

TABLE IV

Kinds of Anaerobes Isolated

Group	RS Method	Th-GP* Method
Bacteroides	Total 59	19
B. fragilis	30	
B. thetaiotaomicron	3	
B. distasonis	5	
B. vulgatis	1	
Bacteroides sp.	Total 20	
Fusobacterium	4	0
F. necrophorum	2	
F. naviforme	1	
Fusobacterium sp.	1	
Anaerobic gram-positive cocci	Total 32	7
S. intermedius	11	
P. asaccharolyticus	8	
S. constellatus	1	
P. magnus	2	
Not speciated	10	
Clostridium	Total 22	14
C. perfringens	6	6
C. ramosum	5	
C. clostridiforme	2	6
Clostridium sp.	9	8
Bifidobacterium sp.	1	0
Lactobacillus sp.	5	0
Propionibacterium sp.	3	0
Other anaerobic nonsporeforming rods	11	3
Veillonella sp.	7	0
Total	144	43

* Species of organisms isolated with the Th-GP method were not determined, except for strains of C. perfringens.

Might have been identified as Bacteroides sp. in the Th-GP method.

Discussion

Laboratory-prepared mixed cultures were used in this study to assure objective evaluation of the Th-GP and RS methods by carefully controlling the number of species of facultative and anaerobic bacteria in each culture and by the elimination of variations inherent in the collection and transport of duplicate clinical specimens. The anaerobes chosen were representative of each of the genera of anaerobes reported to be often isolated from clinical specimens (8–11). The facultative bacteria were those species most often isolated from our patients.

The results of the laboratory-prepared cultures (Table I) demonstrated that the RS method consistently allowed the isolation of the slower growing Eubacterium limosum and Peptostreptococcus anaerobius from mixed cultures containing up to three facultative microorganisms, whereas the Th-GP procedure failed to isolate these organism at all. However, because of the spreading characteristic of Proteus mirabilis, isolated colonies of P. anaerobius were not obtained on RS tubes inoculated with cultures containing these organisms. It is possible that P. anaerobius was present in these RS tubes, but no attempt was made to recover any anaerobe by sub-culture. The Th-GP procedures were only suitable for the isolation of the faster growing Bacteroides fragilis and Clostridium perfringens from cultures containing up to four facultative bacteria. Since selective PEA plates were used in the Th-GP method, the spreading of P. mirabilis was not a factor in the isolation of anaerobes from mixtures containing that organism.

When clinical specimens were cultured, the RS system recovered 117 anaerobes versus 43 anaerobes by the Th-GP procedure ($p < .001$) (Table III). Of the 109 specimens containing anaerobes by RS methodology, 36 proved to be of clinical significance; that is, B. fragilis, F. necrophorum, F. nucleatum, and P. anaerobius were recovered from lesions such as abscesses, peritoneal fluids, wounds, etc., where no other organism was isolated. Furthermore, the patients in these cases responded to therapy directed against these bacteria (complete report to be published at a later date). The Th-GP methodology isolated anaerobes in seven of these 36 specimens.

This study showed that broth procedures are not suitable for the isolation of the slower growing anaerobes. Other investigators have reported similar results with broth media (7, 8).

Direct inoculation of clinical specimens to agar media is considered to be essential to high recovery rates of anaerobes (9, 10, 12, 13). This investigation determined that directly inoculated RS tubes had the major advantage of providing the physician with results at least 24 hours sooner than was possible with GasPak systems, although Rosenblatt et al reported no differences in the species of anaerobes recovered between directly inoculated BAP incubated in GasPak jars and RS tubes (8).

Since each RS tube contains its own anaerobic atmosphere, it could be examined as early and as often as desired without disturbing any other culture, whereas GasPak jars should not be opened for at least 48 hours because exposure to air is deleterious to anaerobes before they have achieved initial growth (11–13). It was often possible to identify the faster growing anaerobes to genus level within 42 hours after the specimen was received in the laboratory, with complete speciation 18 hours later. Slower growing anaerobes required longer time, but the advantage of individual RS tubes permitted detection as soon as these relatively small colonies appeared among the larger and often more numerous facultative bacteria.

In this study, extremely oxygen sensitive anaerobes were not isolated from clinical specimens (Table IV), confirming the findings of others (14). However, evidence indicates that these organisms may not be a cause of clinical infections (8). Nevertheless, the use of RS tubes provides the optimal conditions for these organisms to grow should they, in some instances, prove to be of clinical significance (7, 15). In these cases, longer observation periods would be required, and the RS tubes permit daily examinations for weeks with no loss of anaerobic conditions.

We determined that Th-GP methods are not as suitable as directly inoculated RS tubes for the isolation of anaerobes. RS methodology proved to have two advantages of clinical significance: speed, and the capacity to isolate organisms that would be missed by Th-GP methodology. In addition, there is the capacity to recover even the most oxygen sensitive organisms.

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BETH ISRAEL MEDICAL CENTER

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Beth Israel Medical Center

Introduction

Founded in 1889 to serve the medical needs of thousands of New York's newly arrived immigrants, Beth Israel Medical Center has maintained through the years its original spirit of community service, while constantly increasing the scope of its endeavors. Today, the medical center, which includes Beth Israel Hospital and the Morris J. Bernstein Institute, continues to expand and strengthen its programs in patient care, medical education and research.

There is a major affiliation between the medical center and Mount Sinai School of Medicine. The close integration of clinical departments at Beth Israel and their academic counterparts at Mount Sinai is reflected in teaching of medical students, exchange of house staff and faculty, and coordinated elective programs. The Medical Center actively participates with the medical school in a number of collaborative research and graduate training programs. Second-, third-, and fourth-year medical students follow established programs of assigned and elective studies in most departments of the medical center. Beth Israel physicians and dentists hold appointments at all academic levels on the medical school faculty.

Beth Israel Hospital is a general, acute care, voluntary, non-sectarian institution consisting of three inpatient pavilions and a new inpatient care tower building, plus the Charles H. and Hannah Silver Building for outpatient services. The hospital has over 600 beds and 56 bassinets. Each year there are about 22,000 inpatient admissions, 93,000 outpatient visits and approximately 40,000 visits to the emergency service.

Specialized facilities at Beth Israel Hospital include four intensive care units—medical, surgical, cardiac and neonatal. The hospital's surgical endoscopy unit, one of the largest in the country, is internationally recognized for its pioneering work in the field. Special diagnostic and therapeutic needs of Beth Israel patients are further met by: rehabilitation medicine, nuclear medicine, a cardiopulmonary laboratory, a heart station, thermography and sonar diagnostic equipment and a radiation therapy service that includes an 18-million electron volt linear accelator. A C/T scanner will be available by the beginning of 1979.

Beth Israel has pioneered several noteworthy outpatient programs, including the "I SPY" program for infants and children, the Teenage Service, and the Comprehensive Health Service for adults. In all its ambulatory care programs, Beth Israel places strong emphasis on comprehensive health care and continuity of services.

The Morris J. Bernstein Institute is a 285-bed center for the treatment of psychiatric and addictive diseases. It is the largest voluntary facility in the country for the treatment of drug addiction. Housed in Bernstein are the Drug Detoxification Service (DDS), the central administration of the Methadone Maintenance Treatment Program (MMTP), the inpatient and administrative components of the Alcoholism Treatment Program (ATP), and the inpatient psychiatric unit.

Recognizing that addicted patients often have severe and complex medical problems, Beth Israel has established a medical unit within Bernstein Institute in order to meet these needs. Addicted patients in need of surgical, obstetrical, pediatric, or dental services receive such care. Babies born to addicted mothers receive specialized care in the Beth Israel Hospital nursery.

Beth Israel Medical Center has a house staff of over 200 physicians and dentists who receive broad training in all units of the medical center and in affiliated institutions.

In addition to the care of inpatients, the medical center offers, through its several well-known ambulatory services, a realistic opportunity for a comprehensive approach to the total health needs of a diverse patient population.

In cooperation with academic departments at the Mount Sinai School of Medicine, Beth Israel offers clerkships in all major departments, during which students participate in patient care, seminars, workshops and field projects.

Charles E. Barr, D.D.S.

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Myelolipoma of the Adrenal Gland: Case Report, Literature Review and Analysis of Diagnostic Features

SHIRISH B. DESAI, M.D., LEONARD DOURMASHKIN, M.D., BERNARD R. KABAKOW, M.D. AND
ELLIOT LEITER, M.D.

Abstract

A case of a 54-year-old man with a large left adrenal myelolipoma is presented. The symptom was microscopic hematuria. This is the twelfth reported case, surgically removed. The diagnostic clinicoradiologic features of an adrenal myelolipoma are biochemical nonfunction, radiolucency on plain x-ray, solid nature on sonography, suprarenal mass on intravenous urography, and absence of neovascularity on angiography. The tumor may be symptomatic or asymptomatic. The pathogenesis of adrenal myelolipoma is discussed.

Myelolipoma of the adrenal, a benign nonfunctioning tumor composed of fatty tissue, as well as myeloid and erythroid elements, is a rare lesion, usually found incidentally at autopsy. It was first described in 1905 by Gierke and was given the name myelolipoma by Oberling in 1929 (1, 2). Approximately 160 cases have been described in the world literature. Almost all of these tumors have been small, incidental lesions found at autopsy without antecedent symptoms. The first surgically removed myelolipoma was reported in the Journal of The Mount Sinai Hospital in 1957 (3). We thought it would be appropriate to now report the twelfth case of surgically resected adrenal myelolipoma and review the literature to enhance awareness of this lesion (4–14).

Case Report

M.S., a 54-year-old white male, was admitted with a three-week history of pleuritic pain in the right lower chest and a fluttering sensation of the heart. One week prior to admission, he had been found to have atrial fibrillation. His prior cardiac history was negative. He had smoked three packs of cigarettes daily for many years. There were no urinary symptoms.

Physical examination showed exogenous obesity without cushingoid features. The pulse rate was 65/min and irregularly irregular. The blood pressure was 130/70 mm of Hg. Examination of the lungs and heart was otherwise unremarkable. The abdomen was protuberant and soft. No abdominal masses were felt. There were no other pertinent physical findings.

Complete blood count, blood urea nitrogen, blood glucose, electrolytes, serum calcium, phosphorus, albumin, and arterial blood gases were all at normal levels. Urinalysis revealed 15–20 red blood cells, and a pH of 5. Urine culture was negative. Chest x-ray showed right lower lobe fibrosis (unchanged from x-rays two years previously). EKG showed atrial fibrillation with a rate of 60–70 per minute. Echocardiogram and fluoroscopy showed no evidence of left atrial enlargement. Saphenous venogram showed patent deep calf and femoral veins. Because of a clinical suspicion of pulmonary embolism, the patient was heparinized at the time of admission and placed on oral anticoagulants soon afterwards. Four days after admission, electrical cardioversion of the fibrillation was successfully performed and the patient was then started on Quinidine.

Intravenous urography with tomography (to investigate the microscopic hematuria) showed a large, well-defined, relatively radiolucent mass, 12 cm in diameter, at the superior pole of the left kidney. The kidney was displaced inferiorly (Fig. 1). There were no calcifications. The mass was felt to be extrarenal. The patient had undergone intravenous urography four years before, because of an episode of cystitis. Review of this previous urogram failed to reveal any evidence of a left suprarenal mass. An abdominal aortogram showed a prominent left

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From the Department of Urology, Beth Israel Medical Center, New York, N. Y. 10003.

Requests for reprints should be sent to Shirish B. Desai, M.D., Department of Urology, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, N. Y. 10003.

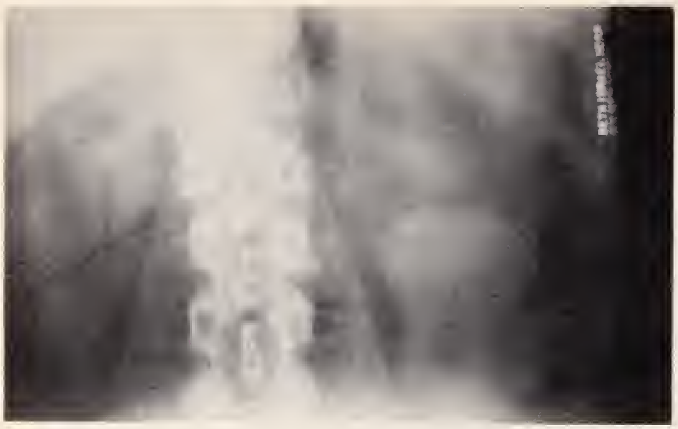

FIG. 1. Intravenous urogram showing mass above displaced left kidney.

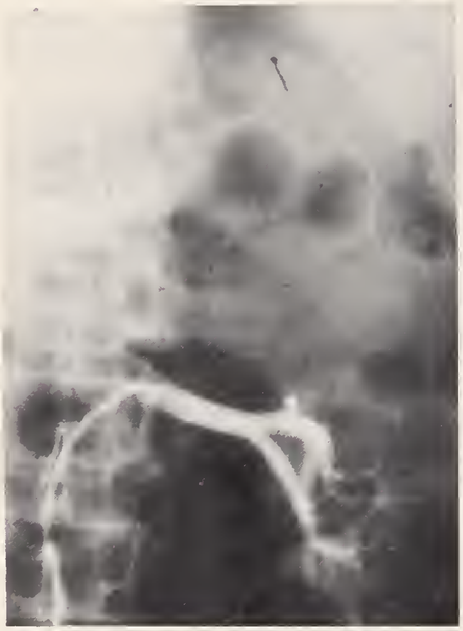

FIG. 2. Left renal selective angiogram showing avascular left suprarenal mass.

middle adrenal artery with scanty vasculature to the presumed adrenal mass. Left renal selective angiogram showed the inferior adrenal artery to be stretched around the avascular mass (Fig. 2). Celiac arteriogram showed normal hepatic, splenic, and pancreatic vasculature. An extremely large adrenal vein with increased venous vasculature was seen on elective left adrenal venography (Fig. 3). No neovasculature was demonstrated. Cystoscopy revealed no bladder abnormalities and clear efflux bilaterally.

Plasma cortisol was 11.9 mg/dl (normal 7–25 mg/dl) in the morning and 8.5 mg/dl in the evening (normal 2–9 mg/dl). Morning cortisol after dexamethasone suppression (1 mg) was 2.8 mcg/dl. Twenty-four hour urinary keto- and hydroxy-steroids were within the normal range. Twenty-four hour urinary vanlylmandelic acid and metanephrine levels were also within the normal range.

The patient underwent exploration of the left adrenal via a left thoraco-abdominal incision through the bed of the tenth rib. There were multiple adhesions between the spleen, greater omentum, and the mass. After retrac-

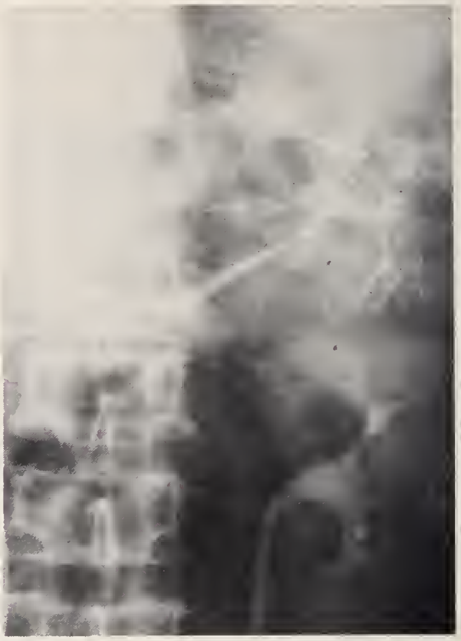

FIG. 3. Left adrenal venogram shows increased venous arborisation.

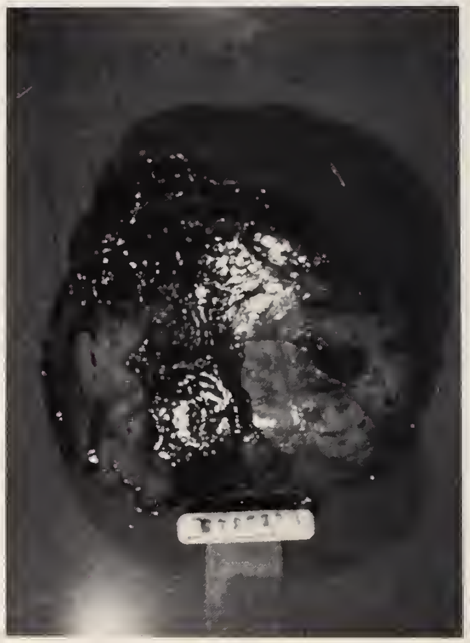

FIG. 4. Gross specimen. Excised left adrenal mass.

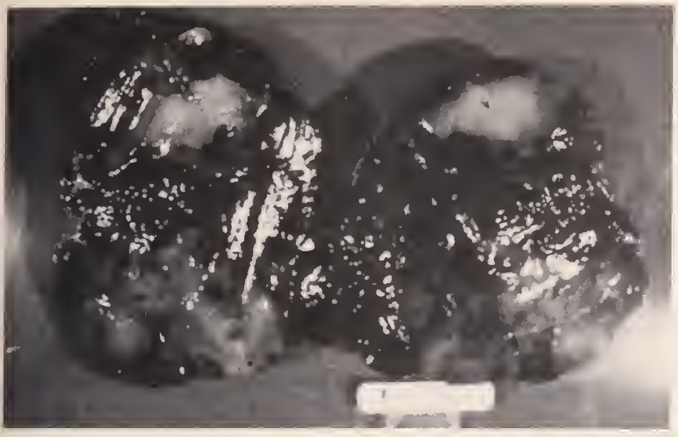

FIG. 5. Cut section of gross specimen.

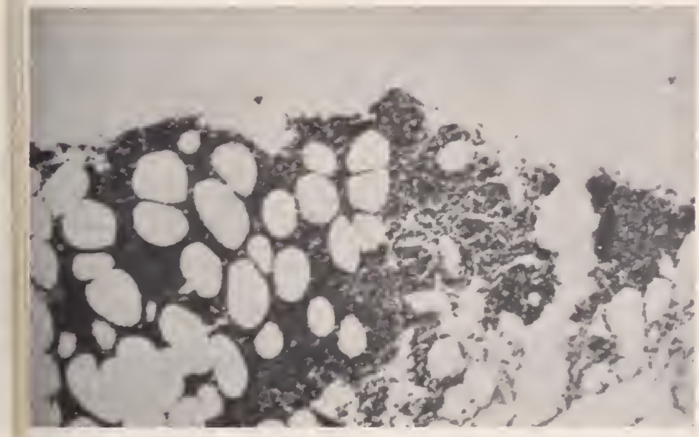

FIG. 6. Microscopic section showing haematopotic elements.

ion of the left colon, there was a 10.5 × 8 × 6 cm mass een in the left suprarenal area. The mass, together with he attenuated adrenal gland lying over it, was easily issected and removed. The patient's postoperative ourse was unremarkable. He has had no further microcopic or gross hematuria. Eighteen months postoperaively he remains well.

The specimen was a large spherical, soft, yellow-red ass weighing 360 grams and measuring 10.5 × 8 × 6 ms (Fig. 4). On cut surface, it was smoothly lobulated ith reddish and yellowish areas (Fig. 5). A thin rim of drenal tissue, measuring 3 × 2 cms, was noted at its eriphery. Microscopic examination showed adipose tisue with several areas of hemorrhage and necrosis (Fig.). Scattered throughout the adipose tissue were areas of ematopoietic bone marrow elements.

Discussion

Adrenal myelolipoma is an uncommon tumor comosed of hematopoietic and fatty tissue. It is rarely seen inically. The reported incidence at autopsy ranges from 0.08 to 0.2% (10). The tumors vary in size from microscopic foci to 8 cms. They are most commonly demonstrated at the fourth to seventh decades. They have never been reported before puberty. In the past there have been no apparent sex predilection. Most of the masses are unilateral, though a few bilateral cases have been described.

There have been only eleven prior instances of surgical removal of adrenal myelolipoma. The clinical features of these cases are summarized in Table I. Their ages are from 41 to 67 years. Males have a 2:1 predilection over females. There were six tumors each on the left and right sides. In ten out of the twelve cases the body habitus was described robust, obese, or well developed. Eight out of the twelve patients were hypertensive.

In no instance was the diagnosis of myelolipoma of the adrenal gland made preoperatively. In fact, it was never even considered in the differential diagnosis. Hence, we thought it worthwhile to analyze their various clinical symptoms and radiographic findings, to see if we could gain any insight that would aid in future diagnosis.

The presence of a suprarenal mass was first appreciated in each instance on intravenous urography. Seven of the twelve patients had flank or abdominal pain that was probably related to hemorrhage or necrosis in the tumor (3–5, 7, 8, 12, 13). In the five asymptomatic cases, four had gross or microscopic hematuria, and one patient underwent work-up for hypertension (6, 9–11). The hematuria was apparently secondary to a concomitant hypernephroma in one case and to calculous disease in two other patients (6, 9, 10). In the other two patients with hematuria, as well as in our case, no cause for the hematuria was found.

Adrenal function tests done in nine out of the twelve cases were all normal, with no biochemical evidence of hyperfunction. Intravenous urography showed radiolucent masses in the suprarenal area often pushing the kidney inferiorly. Indeed, if a nonfunctioning adrenal mass is radiolucent on the plain film, implying a fatty stroma, the diagnosis is almost certain (11). Arteriography performed in five cases generally showed an avascular mass with adrenal vessels stretched over it. One patient had multiple angiomas in the liver and in the lumbar spine (9). Venography has been done in only two cases–these again showing no suggestion of malignancy (10, 11). In addition to our case, sonography is described only once before and it clearly showed a solid mass (11). The diagnosis of cyst can thus be definitely excluded. I^{131}-19 Iodocholesterol scan was reported on one case–this showed no evidence of adrenal function, despite identification of normal adrenal in the specimen (11).

Hence a biochemically nonfunctioning, radiolucent solid adrenal mass with no neovascularity on angiography is likely to be an adrenal myelolipoma.

TABLE I

Myelolipoma Operatively Removed

Author's	Age	Sex	Side	Body habitus	Blood pressure	Presentation	Urologic disease	Specimen Wt	Diameter measure.	Calcification
Dyckman & Freedman	47	M	Rt	—	116/94	pain	—	1100*	16 cm	—
Parsons & Thompson	51	F	Rt	obese	140/90	pain	—	1250*	25 cm	—
Figueroa & Tedeschi	67	F	Rt	—	—	pain	—	?	?	—
Engelking et al	63	M	Rt	obese	—	hematuria	renal cancer	?	10 cm	—
Newman & Silen	41	M	Lt	robust	140/90	pain	—	?	18 cm	bilateral calcification
Whittaker	57	F	Lt	obese	154/98	pain microhematuria	—	?	7 cm	calcification
Tulcinsky et al	53	M	Rt	well nourished	190/120	hematuria	calculus	850*	20 cm	—
Olsson et al	44	M	Lt	obese	180/90	hematuria	calculus	440*	—	—
Gee et al	43	M	Rt	obese	180/126	hypertension	—	312*	7.5 cm	
Rubin et al	49	M	Rt	well developed	155/100	pain	—	50*	6 cm	bilateral
Snearly et al	46	F	Lt	obese	120/70	pain	—	140*	8 cm	bilateral
Desai et al	54	M	Lt	obese	130/70	microhematuria	no cause found	360*	10.5 cm	—

* grams

Treatment has consisted of excision of the mass with the adrenal gland. There have been no reports of recurrence. Nephrectomy was performed in two cases, and is probably unnecessary (3, 10). Certainly, it could have been avoided if the diagnosis had been considered preoperatively or intraoperatively.

Pathologically these tumors should be distinguished from extramedullary hematopoiesis and ectopic bone marrow formation (14). Myelolipoma consists of myeloid and fat cells with reticulum cells in the fatty areas. In extramedullary hematopoiesis only myeloid cells are found. Ectopic bone marrow has calcification and bone formation. The tumor is believed to arise in the inner half of the zona fasciculata (14). Extraadrenal myelolipomas have also been described; but these are, in contrast to adrenal myelolipoma, always associated with blood dyscrasias such as severe anemia, leukemia (15). No hematologic disorder is apparently associated with adrenal myelolipoma.

Several theories have been proposed to explain the etiology of myelolipoma (16). The earlier theories included embryonic bone marrow rests, embolism of bone marrow cells, extramedullary hematopoiesis, and simple hamartoma. The theory that has gained most support proposes metaplasia of the reticulum cells. Selye and Stone were able to induce myelolipomatous changes in the adrenal glands of rats by injecting crude anterior pituitary extract, thyroxin and testosterone (14). They believed that these changes were similar to those occurring in man and associated with "disease of general adaption," that is, advanced carcinoma, arteriosclerosis, nephropathies, and hypertension. Olsson felt that the stimulus for metaplasia was probably tumor necrosis or necrosis of normal tissue in response to trauma or impaired circulation (10).

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Adjuvant Immunotherapy for Vulvar Malignant Melanoma

ROBERT C. WALLACH, M.D. AND ROBERT N. TAUB, M.D., Ph.D.

Abstract

Malignant melanoma of the vulva is usually treated by radical surgery, but even in early cases, the chances for cure are small. A 23-year-old patient with this disease underwent surgery and was then treated with adjuvant immunotherapy. She is clinically free of disease four years later. The technique and rationale for adjuvant immunotherapy are described and this treatment is advocated for malignant melanoma of the vulva.

Introduction

Aggressive surgery is the basis of treatment for melanoma of the vulva (1–4). Radical vulvectomy and bilateral groin lymphadenectomy constitute the basic minimum treatment. Deep pelvic lymphadenectomy, excision of the lower vagina and/or urethra, or exenteration may be added for extensive disease and cryosurgery has been used in selected cases (5). Chemotherapy has also been added to the therapeutic attack on this disease (6–8). However, despite aggressive surgery and the use of antitumor drugs and irradiation, the anticipated survival is poor, and the need for more effective therapeutic measures is great (9, 10).

In an attempt to improve the outlook for a patient following surgery for this disease, adjuvant immunotherapy has been added to the treatment. Adjuvant refers to a foreign material used for nonspecific stimulation of the reticuloendothelial system, such as Freund's adjuvant, rather than the addition of radiation, chemotherapy, and/or immunotherapy to surgery. We have not found a eport of adjuvant immunotherapy for melanoma in a emale genital site and believe this to be the first such reatment.

Case Report

A 23-year-old Para 1001 underwent a routine gyneco-ogic examination and was found to have a 0.5 cm pigmented lesion of the inner aspect of the left labium minus. Excisional biopsy of the lesion revealed malignant melanoma. Diagnostic studies including routine blood analyses, x-rays, lymphangiography, and isotopic scans revealed no evidence of disseminated disease. On January 23, 1975, the patient underwent radical vulvectomy and bilateral groin lymphadenectomy. No residual disease or involved lymph nodes were found. Subsequent to discharge the patient was started on a course of adjuvant immunotherapy with methanol-extraction residue of BCG (MER). An intradermal dose of 0.25 mg MER was given to each extremity (total dose 1.0 mg) and repeated monthly for 18 courses. Repeated skin testing with intermediate-strength tuberculin (P.P.D.) was negative through the course of treatment. One year following initial surgery, the patient detected several pigmented areas around the anus. Multiple biopsies revealed benign intradermal nevi. There is no evidence of recurrent disease and the patient is well, four years later.

Discussion

The prognosis for a patient with melanoma of the vulva is poor but difficult to predict. The radical surgical approach to disease of the vulva is appropriate since the local and regional tissues and first stage lymph nodes can be removed en bloc. Radical vulvectomy and lymphadenectomy is the generally accepted management for this disease, with extended operations for advanced local disease. Because of the infrequency of this disease entity, improvements in therapy will be difficult to evaluate, but the suggestion of improved salvage for melanoma of other sites treated with adjuvant immunotherapy led to its use in this patient (11).

The use of immunopotentiating agents such as BCG and MER in the treatment of human cancer is predicated on the idea that tumor cells express different cell surface

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From the Department of Obstetrics & Gynecology, Beth Israel Medical Center, N. Y., and the Department of Oncology, Medical ollege of Virginia, Richmond, VA.

antigens than those of their normal counterparts, and that a host response can be mounted toward the abnormal antigen. Such tumor-specific antigens have been plausibly demonstrated in malignant melanoma. BCG vaccine has been given by intradermal inoculation as a nonspecific immunologic adjuvant, or by direct injection into melanotic lesions. A number of investigators showed clinical regression of local lesions (12–16). Other investigators showed regression of systemic disease following immunotherapy with BCG (17, 18). Recently a number of studies performed by Weiss et al in Jerusalem have shown that the methanol-resistant fraction of BCG (MER) can also act as a potent immunological adjuvant, with the additional advantage that it is not as likely to cause disseminated disease as the live BCG vaccine (19, 20).

With major reported series of treated cases of vulvar melanoma including frequencies of less than two cases per year, assessment of the impact of adjuvant immunotherapy is difficult; but with conventional surgical therapy yielding poor salvage, the addition of immunotherapy should be considered in all such cases.

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Amyloidosis in Parenteral Drug Abusers

DAVID M. NOVICK, M.D., STANLEY R. YANCOVITZ, M.D., AND PATTI G. WEINBERG, B.A., P.A.-C.

Introduction

Amyloid deposition has not been noted as a common accompaniment of parenteral drug abuse or of the associated cutaneous infections of drug abuse. Only recently have several reports of amyloidosis as a cause for nephrotic syndrome in narcotic addicts emerged (1–3). This report concerns two heroin abusers we have encountered with documented amyloidosis, massive proteinuria, and numerous localized skin infections. We believe that amyloidosis may be more common in the addict population than generally appreciated. Its occurrence in this population may lead to significant theoretical and practical considerations.

Case Report

Patient 1: J.D., a 36-year-old Black male, was referred to the medical service of the Morris J. Bernstein Institute (MJBI) in December 1976, for evaluation of proteinuria. He had been injecting heroin intravenously several times a day since age 21. He intermittently abused cocaine intravenously as well as valium and illicit methadone orally. He had previously been detoxified with methadone at MJBI in 1963, 1972, May 1976, and October 1976. On each of these occasions antibiotics were prescribed for skin infections. In 1972, he had multiple healed ulcerations of all extremities, lymphedema of both upper extremities, and an infected ulcer on the left forearm. Later that year he sustained a burn on the inferolateral aspect of the left leg which became intermittently infected and never healed—despite nine attempts at skin grafting at three other hospitals. In 1975, he entered a methadone program but left it in February 1976, and resumed parenteral drug abuse. Proteinuria was noted for the first time in October 1976. In December 1976, he noted swelling of the face and legs. There was no previous history of tuberculosis, endocarditis, hepatitis, arthritis, or pulmonary or renal disease.

Physical examination disclosed fresh puncture wounds on both forearms, lymphedema of all extremities, and a "U"-shaped, nongranulating ulcer surrounding a skin graft on the inferolateral aspect of the left leg. The remainder of the examination was normal except for a grade II/VI systolic ejection murmur at the apex.

Pertinent laboratory data included a hematocrit of 35.6% and a normal white blood cell count and differential. Urinalysis revealed specific gravity of 1.022, 4+ protein, and negative glucose. The BUN was 16 mg/dl; the creatinine was 1.4 mg/dl; the total protein was 6.7 g/dl; the albumin was 3.1 g/dl; and the cholesterol was 298 mg/dl. The 24-hour urinary protein excretion was 10.6 g. Serum protein electrophoresis showed elevations of the α_2, β, and γ globulin fractions with no M-component. VDRL, latex fixation, and antinuclear antibodies were negative. The erythrocyte sedimentation rate was 67 mm/hour; serum C3 was normal, and serum C4 was 52 mg/dl (normal 20–40). The electrocardiogram, chest roentgenogram, and intravenous pyelogram were normal. Roentgenogram of the left leg disclosed soft tissue ulceration, shaggy periosteal bone along most of the medial and lateral fibula shaft, and cortical thickening of the lower lateral portion of the fibula shaft. Urine protein electrophoresis showed 70% albumin and 30% globulins. Serum immunoelectrophoresis revealed no abnormal proteins. Gingival biopsy was negative for amyloid, and the patient refused renal biopsy.

He returned to MJBI in July 1978, complaining of recurrent facial puffiness. He had abused heroin until March 1978, when he became a successful participant in a drug-free program. Physical examination was unchanged. The BUN was 23 mg/dl; the creatinine was 3.2 mg/dl; the 24-hour urinary protein excretion was 15 g; the creatinine clearance was 46.3 ml/min; the serum albumin was 2.7 g/dl. Renal biopsy was performed in August 1978. The specimen for light microscopy contained no glomeruli, but amyloid deposition was seen in tubular basement membranes on routine and polarization microscopy. Electron microscopy was diagnostic for amyloidosis (Fig. 1).

From the Department of Medicine, Morris J. Bernstein Institute, Beth Israel Medical Center, New York, N. Y. 10003, and Mount Sinai School of Medicine of The City University of New York, New York, N. Y. 10029.

Requests for reprints should be sent to David M. Novick, M.D., Morris J. Bernstein Institute, Beth Israel Medical Center, 307 Second Avenue, New York, N. Y. 10003.

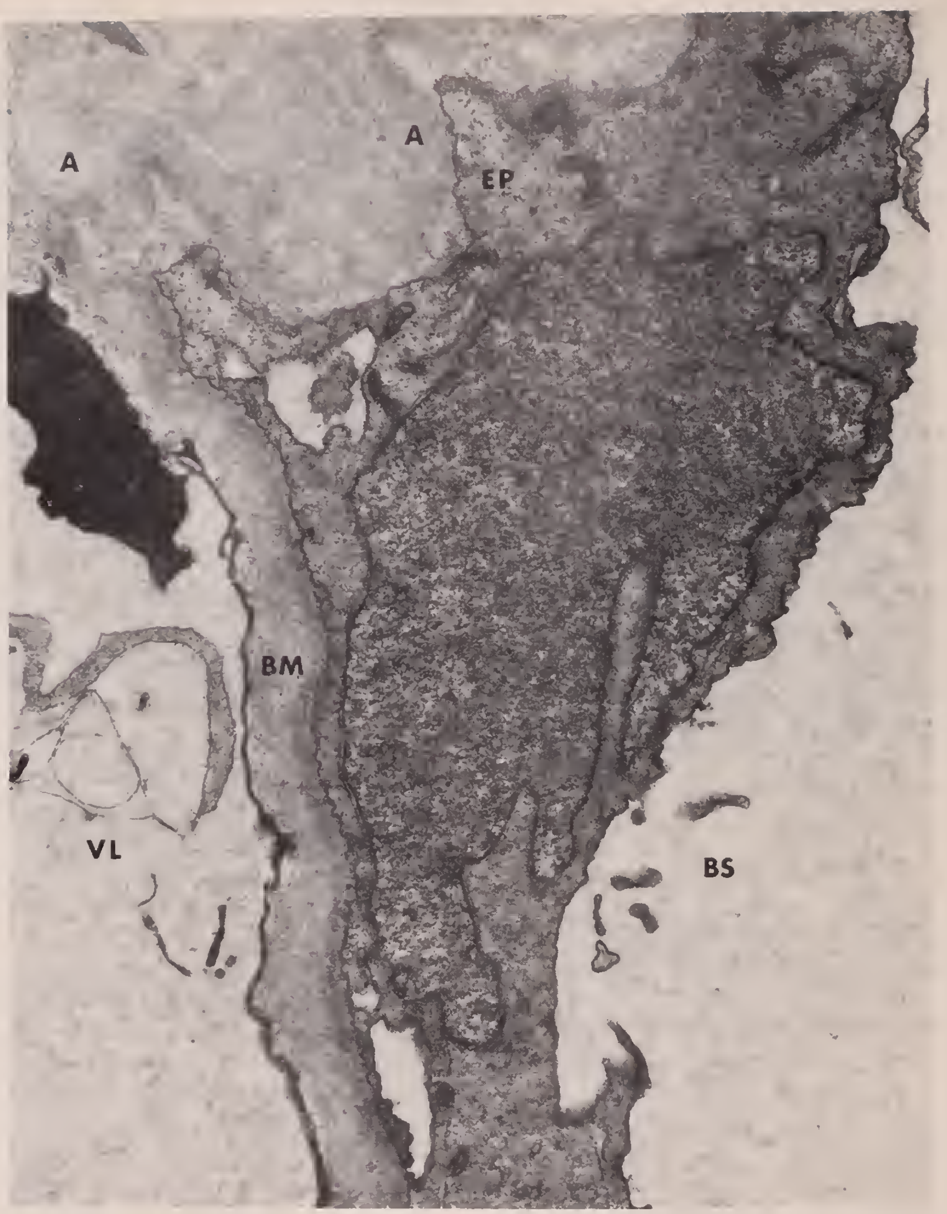

FIG. 1. Electron micrograph of glomerulus from renal biopsy in Patient 1. Amyloid fibrils are seen in the basement membrane, contiguous with a large collection of amyloid. Amyloid fibrils (A), basement membrane (BM), epithelial cell (EP), Bowman's space (BS), vascular lumen (VL) (×13500).

In October 1978, he was readmitted to MJBI for intensive local therapy to the skin ulcer and further studies. A bone scan revealed no evidence of osteomyelitis. A bone marrow aspirate was normal. An intermediate strength PPD was positive; chest and apical lordotic roentgenograms were normal, and no sputum was produced. Urine immunoelectrophoresis showed large amounts of albumin, α and β globulin, and intact immunoglobulins IgA and IgG. The leg ulcer showed significant healing.

Comment: This patient developed renal amyloidosis following 15 years of heroin abuse associated with chronic recurrent skin infections. Osteomyelitis underlying a large infected skin ulcer may have been present previously, but only soft tissue infections were documented.

Patient 2: L.B., a 40-year-old Black male was admitted to MJBI in January 1978 for detoxification from heroin and evaluation of hematuria and proteinuria. He had been abusing heroin and cocaine intravenously multiple times per day for 20 years. Previously, he had been admitted on seven separate occasions for heroin detoxification between 1975 and 1977. On all prior admissions he had infected cutaneous ulcers on the extremities requiring antibiotic therapy. Microscopic hematuria without proteinuria was noted on two previous admissions in

February 1977, and August 1977. An intravenous pyelogram done in August 1977, was normal. He also had anemia attributed to chronic disease on previous hospitalizations. There was no history of tuberculosis, osteomyelitis, endocarditis, arthritis, or renal disease.

Physical examination on admission disclosed fresh puncture wounds on both upper extremities. Lymphedema was present on all four extremities and was prominent in all but the right arm. Multiple healed abscess scars were noted and multiple fresh cutaneous ulcers were present on the left arm and both legs (Fig. 2). Two ulcers on the left forearm appeared necrotic. The patient was afebrile, and the rest of the physical examination was normal.

Pertinent laboratory data included a hematocrit of 31.6% with normal WBC count and differential. Urinalysis revealed specific gravity of 1.012, 4+ protein, and large occult blood. Hyaline, granular, and white cell casts were seen in the sediment. The BUN was 22 mg/dl; the creatinine was 2.5 mg/dl; the total protein 6.0 g/dl; the albumin 2.8 g/dl; and the cholesterol 247 mg/dl. Urine cultures for routine pathogens and acid-fast bacilli were negative. Blood cultures were negative. Wound cultures grew Escherichia coli and Staphylococcus aureus. 24-hour urine showed 8.4 g of protein. Urine protein electrophoresis disclosed 52% albumin and 48% globulins. Serum protein electrophoresis showed no M-component, a slight decrease in the α_1, and a slight increase in the α_2, β, and γ globulin fractions. Urine immunoelectrophoresis revealed no abnormal proteins or free light chains. Intact IgA and IgG with both lambda and kappa chains were present. Serum immunoelectrophoresis showed normal levels of IgG, IgM, and IgA. VDRL, HB_sA_g, latex fixation, and antinuclear antibodies were negative. Serum C_3 and C_4 were normal. The erythrocyte sedimentation rate was 41 mm/hour.

Renal biopsy disclosed amyloidosis on light, polarization, and electron microscopy (Fig. 3). Rectal biopsy was negative for amyloid. Bone marrow examination showed no evidence of myeloma. Gallium scan revealed no evidence of osteomyelitis and no visualization of the kidneys. An intermediate strength PPD was positive, but sputums for acid-fast bacilli were negative. Roentgenograms of the chest were normal. Bone roentgenograms revealed soft tissue swelling but no evidence of osteomyelitis. Appropriate antibiotics were given for the cutaneous infections. The patient was referred to a methadone maintenance treatment program after diagnostic procedures were complete. He accepted this therapy after multiple previous refusals, and, subsequently, he substantially reduced the frequency of his intravenous drug abuse.

Comment: This patient had renal amyloidosis and nephrotic syndrome. An extensive diagnostic evaluation excluded all other causes for the amyloid deposition except for multiple cutaneous infections and chronic parenteral heroin abuse.

Discussion

In both of our patients, systemic amyloidosis developed after prolonged intravenous heroin abuse. Both patients had renal involvement with massive proteinuria, although the initial manifestation of Patient 2 was microscopic hematuria. Neither patient had an enlarged tongue, a positive rectal or gingival biopsy, or evidence of cardiac involvement. This distribution of amyloid in-

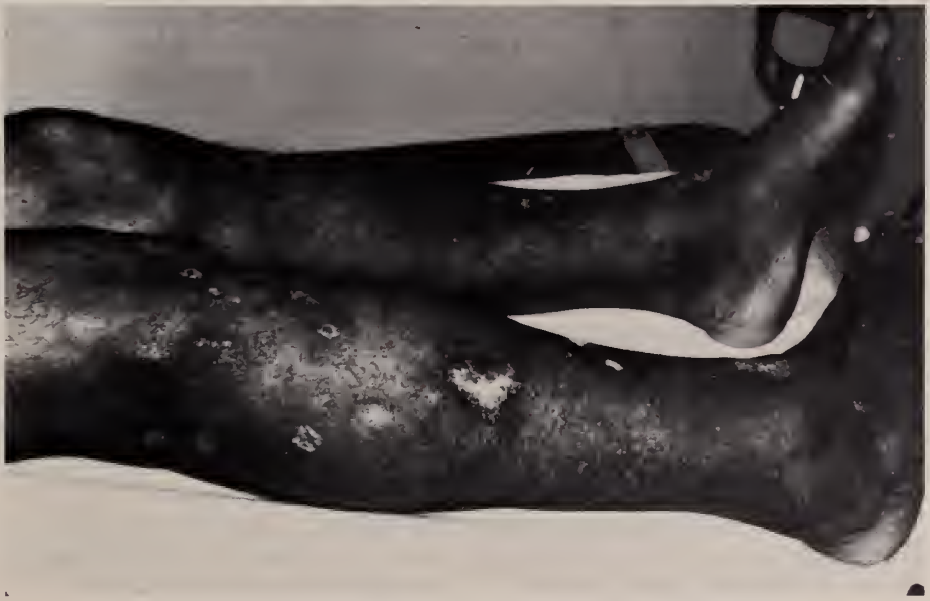

Fig. 2. Multiple healed abscess scars and the lymphedema of both legs of Patient 2.

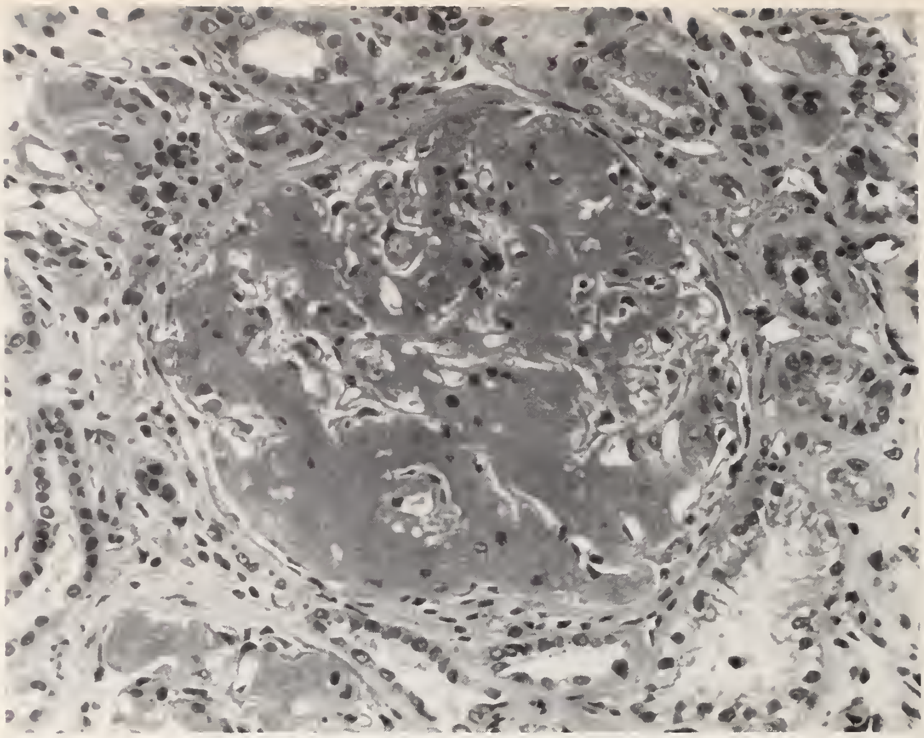

FIG. 3. Representative glomerulus from Patient 2 showing extensive amyloid deposition. (Hematoxylin and eosin, ×230).

filtration is consistent with secondary amyloidosis, as is the absence in both patients of monoclonal proteins in the serum and urine. Kyle and Bayrd have reported monoclonal proteins in 58% of patients with primary amyloidosis and in 89% of patients with amyloidosis and multiple myeloma (4). Neither patient had significant abnormalities on bone marrow examination or clinical evidence of a plasma cell dyscrasia.

The usual chronic infectious and inflammatory disorders that are complicated by amyloidosis were not present in our patients (5, 6). Among these entities, tuberculosis and osteomyelitis are most likely to be seen in the drug addict (7, 8). Although both patients had positive tuberculin tests, their chest roentgenograms were normal and they had no signs or symptoms of tuberculosis. Patient 1 had equivocal evidence of previous osteomyelitis.

The most likely stimulus for the development of amyloidosis in both of our patients was the extensive cutaneous suppuration caused by their parenteral drug abuse. Both patients had multiple chronic skin abscesses and resulting lymphedema of the involved extremities. Two other reports have implicated skin infections as a cause of amyloidosis in the drug addict (1, 2). Systemic amyloidosis has been described rarely as a sequela of other infected dermatologic conditions, including stasis ulcers, hidradenitis suppurativa, and dystrophic epidermolysis bullosa, thermal burns, and decubitus ulcers (9–12).

An additional common factor in both patients is sustained intravenous heroin abuse for 15 or more years. Prior to the onset of the nephrotic syndrome, both were refractory to therapeutic intervention for their drug abuse. Such prolonged heroin abuse may be a form of chronic antigenic stimulation, which is a unifying characteristic of several types of clinical and experimental amyloidosis (13). Several factors could contribute to this antigenic load. Heroin is diluted with a variety of adulterants and is dissolved in water that is often contaminated (14, 15). The syringes and needles are used repeatedly and are generally not sterilized between injections. During the injection itself, aseptic technique is rarely employed. Heroin abusers are subject to a wide range of infectious complications, including cutaneous abscesses, pneumonia, endocarditis, viral hepatitis, and venereal diseases (15, 16). Presumably, chronic antigenic stimulation in addicts causes the commonly noted increased serologic reactivity, such as false positive VDRL reactions, elevated febrile agglutinins, increased latex fixation titres, and elevated immunoglobulin levels (17). Furthermore, generalized lymphadenopathy is common in drug addicts and has been attributed in some cases to a nonspecific response to intravenous injection of narcotics (18). It seems likely, therefore, that the intravenous infusion of antigens in heroin abuse could augment the formation and deposition of amyloid if sustained for a sufficiently long period. However, the precise role of heroin abuse per se in the pathogenesis of amyloidosis in our patients remains unclear.

Amyloidosis has rarely been described as a consequence of drug addiction (1–3). Two addicts with amyloidosis have been reported in whom no connection between their amyloid infiltration and drug abuse was noted (19, 20). One of these patients also had culture negative bacterial endocarditis and a lung abscess, but no cutaneous infections (19). Our findings of two drug addicts in less than one year with the diagnosis of renal amyloidosis suggests that this complication may be more common than previously considered.

Heroin addicts with nephrotic syndrome have been shown to have a variety of glomerular lesions, most commonly focal sclerosis (15, 21). Addicts with so-called heroin associated nephropathy appeared to be different from our patients with amyloidosis in that their age was most likely to be in the second or third decade, and their duration of heroin abuse was sometimes as short as one year (22). We suggest that amyloidosis be considered prominently in the differential diagnosis of the heroin addict with nephrotic syndrome, particularly if the duration of heroin abuse is prolonged. Evidence of chronic cutaneous suppuration in a drug abuser with massive proteinuria should also suggest renal amyloidosis.

The therapy of secondary amyloidosis remains as intensive treatment of underlying diseases (23). In the drug addict, placement in an appropriate drug-free or methadone maintenance program should be attempted. Recognition of a serious medical problem may render the addict more compliant to such therapy, and it is perhaps a hopeful note that both of our patients have substantially reduced their drug-abusing behavior following their evaluation for nephrotic syndrome.

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Prolonged Neonatal Cholestasis: Bile Acid Pattern and Response to Cholestyramine

JOSEPH S. LEVY, M.D., ALVIN M. GELB, M.D., RICHARD J. STENGER, M.D., AND
NORMAN B. JAVITT, M.D., PhD.

Abstract

A neonate with cholestatic jaundice showed a spontaneous improvement in liver function tests except for serum bile acids which remained markedly abnormal. Liver biopsy showed early parenchymal changes with portal fibrosis and bile duct proliferation by ten weeks of age. Bile acid binding resin therapy was followed by reduction of serum bile acids and a dramatic reversal of the abnormal hepatic morphology. Subsequently, the levels of serum bile acids served as a useful guide to the need for reinstituting therapy. We suggest that serum bile acid monitoring may effectively guide the use of bile acid binding resin therapy in neonatal cholestatic jaundice.

Introduction

Prolonged cholestasis in the neonatal period requires the consideration of extrahepatic biliary atresia since surgical intervention is potentially helpful in certain patients. Unlike obstructive biliary tract disease in the adult, the biliary tree proximal to the obstruction is not dilated in neonates and, therefore, procedures such as sonography are not as useful in distinguishing atresia from cholestatic syndromes with patent ducts. Also, newer procedures such as endoscopic retrograde cholangiography and thin-needle percutaneous cholangiography have not been established as useful measures in this age group. Therefore, during the neonatal period, the problem of medical versus surgical jaundice still depends primarily on clinical and laboratory evaluation together with interpretation of the liver biopsy.

An infant, born at Beth Israel Medical Center developed severe neonatal cholestasis that could not be distinguished from biliary atresia on clinical evaluation and routine laboratory tests. Because the initial and subsequent liver biopsies were not characteristic of extrahepatic biliary atresia, it was decided to place the infant on cholestyramine therapy to obtain further diagnostic information (1). Improvement in the results of laboratory tests was followed by lessening of cholestasis and return of liver morphology toward normal.

Our experience with this infant, particularly with the use of serial serum bile acid determinations, may be useful to others caring for infants with this difficult problem.

Case Report

This male infant was the 4 kg product of the normal third pregnancy of a Hispanic mother with no prenatal history of infections or exposure to drugs or toxins. There was no family history of liver disease. Delivery by Cesarian section was followed by severe meconium aspiration pneumonia. Intensive respiratory therapy was given during the first 48 hours of life with improvement. He received matched transfusions to compensate for blood samplings. No Rh or ABO incompatibilities were present.

At age four days, total bilirubin was 6.0 mg/dl with 0.2 mg/dl direct reacting. Jaundice was present and persisted. At age eight days, the bilirubin had increased to 7.5 mg/dl. Hemoglobin was stable. Vomiting occurred when oral feedings were introduced. A firm liver was palpable 5 cm below the costal margin. A rubbery spleen was palpable 4 cm below the costal margin. At age 14 days, total bilirubin was 8.8 mg/dl, 6.5 mg/dl direct.

Initially, the urine was positive for urobilinogen at 1:64 dilution. Subsequently, the concentration of urine urobilinogen decreased and finally disappeared by age 20 days.

At three weeks of life, the SGOT was 510 U/ml (normal 4–40 U/ml), the SGPT 420 U/ml (normal 3-36 U/ml), and the alkaline phosphatase was greater than 353 IU/ml (normal 156-241 IU/ml). Total serum protein was 7.3

From the Departments of Pediatrics, Medicine and Pathology, Beth Israel Medical Center, New York, N. Y., and Division of Gastroenterology, Cornell Medical Center, New York, N. Y.

Requests for reprints should be sent to Alvin M. Gelb, M.D., Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, 10003.

g/dl; albumin was 4.6 g/dl; gamma globulin was 2.7 g/dl. Immunoglobulin concentrations showed a slightly elevated IgG of 1780 ug/dl (normal 750-1650 ug/dl); other fractions were within normal limits.

Blood and urine cultures were negative; HBsAg was negative in both infant and mother. The RPR test for syphilis was nonreactive. Urine and blood amino acid screens were negative. Titers for cytomegalic inclusion virus, rubella, and herpes virus were within normal limits. Alpha-1 anti-trypsin was 300 units, normal being 200-400 units. Alpha feto-protein was positive (normal reference for the laboratory is nondetectable); 5′ nucleotidase was 1.0 IU/dl. (normal 0-16 IU/dl). A I^{131} Rose Bengal test at age three weeks revealed less than 0.1 percent of the isotope in a three-day stool collection, with no counts over the bowel up to 96 hours after injection.

A percutaneous liver biopsy, performed at age three weeks showed centrilobular cholestasis with canalicular plugs, occasional mutlinucleated, giant liver cells and prominent reticuloendothelial elements. Moderate inflammatory infiltration was present in the portal areas, where rare intact bile ducts and ductules were found with difficulty. No bile duct duplication was seen.

At age six weeks repeat liver biopsy showed a marked increase in the number of parenchymal giant cells, but reduced cholestasis. Extensive ballooning degeneration and occasional acidophilic bodies were seen, and small bile ducts were evident in the portal areas. Slight portal fibrosis had developed.

At two months of age the bilirubin had decreased to 4.9 mg/dl with 3.6 mg/dl direct reacting. The SGOT and SGPT were 314 U/ml and 249 U/ml respectively. Urobilinogen had reappeared in the urine. HBsAg was still negative, and the alpha-1 antitrypsin level was still within the normal range. Latex fixation and antinuclear antibody were negative.

At age ten weeks, the third liver biopsy again showed many giant cells, but there was a progression of the hepatitic process with prominent inflammatory infiltration of the portal areas and fibrotic bridging between portal triads. There was little change in the amount of cholestasis or reticuloendothelial cell activation. Ballooning degeneration and acidophilic bodies were still seen (Fig. 1).

Although liver enzymes remained elevated, the bilirubin slowly decreased to about 4 mg/dl, mostly direct reacting, and remained at that level. At age 12 weeks treatment with cholestyramine was started at a dose of 8 gm daily in two doses (Fig. 2).

Serum bile acid analysis performed before therapy showed an increase in total bile acids to 144 μg/ml (normal less than 6 μg/ml), and a reversal of the normal cholic acid/chenodeoxycholic acid ratio of greater than one. Two weeks after the institution of therapy, there

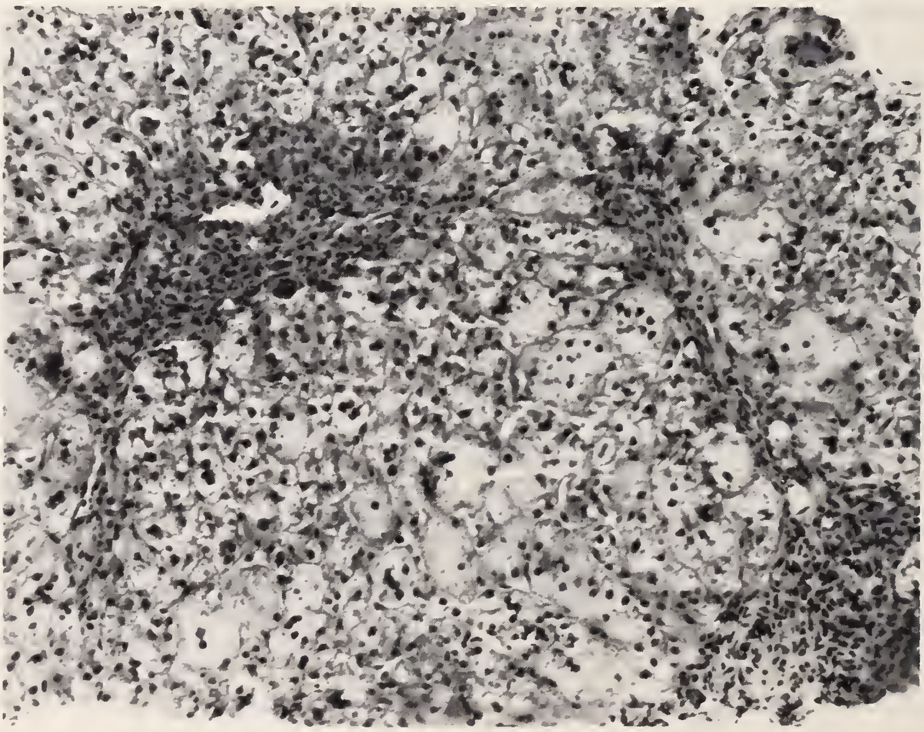

FIG. 1. Light micrograph of a representative field from the third liver biopsy. The portal areas are expanded by inflammatory infiltrates a proliferating fibroblasts. Tenuous fibrous bands tend to link together the portal tracts. The parenchymal cells are swollen and many a multinucleated, the Kuppfer cells are hypertrophic. Hematoxylin and eosin stain. ×70.

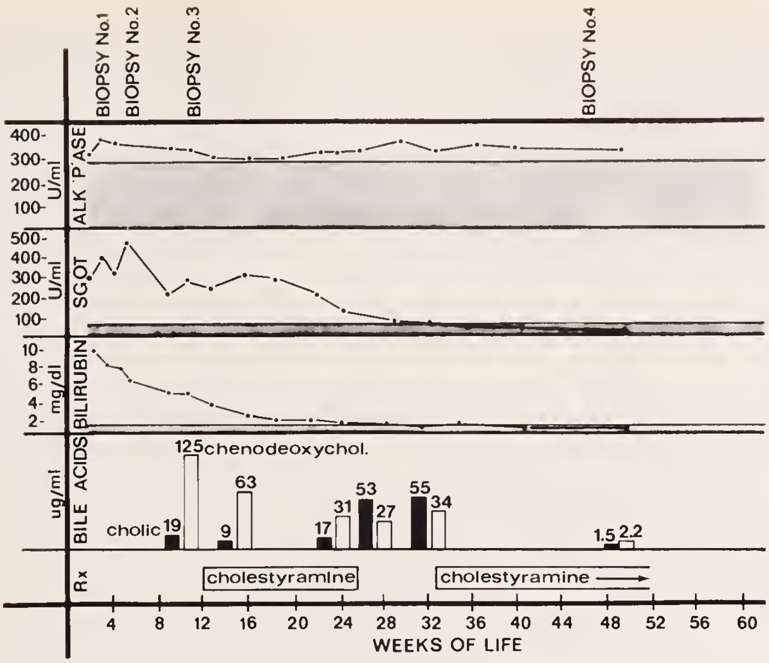

FIG. 2. The effect of cholestyramine on liver function tests and serum bile acids.

was a marked decrease in the chenodeoxycholic acid level from 125 μg/ml to 63 μg/ml (normal below 0.2 μg/ml) and of cholic acid from 19 μg/ml to 9 μg/ml (normal below 0.9 μg/ml). Concomitant with the administration of cholestyramine, the previously pale stool became green, and the serum bilirubin continued to decrease. After 12 weeks of treatment, it was 2 mg/dl. A repeat I^{131} Rose Bengal test at age five months showed persistent and marked retention of the isotope in the liver but there was also evidence of excretion of isotope into the small bowel.

At age six months, when the cholestyramine was stopped because of feeding problems, serum bile acids showed that a further decrease had occurred. The chenodeoxycholic acid was 34 μg/ml, one-fourth of the pretreatment level, and the cholic acid had increased to the pretreatment level (17 μg/ml).

During the two months without cholestyramine, the serum bilirubin fell to normal, and the SGOT and SGPT rapidly improved, a trend that had started in the middle of the cholestyramine therapy. However, the serum bile acids increased and pruritus developed. Therefore, a second course of cholestyramine was started at age eight months.

At age 13 months the infant was thriving, growth and development were normal, and pruritus had decreased. Bilirubin, SGOT and SGPT were normal, although the alkaline phosphatase remained slightly elevated. Serum bile acids had decreased; cholic acid was 13 μg/ml. Chenodeoxycholic acid was 3 μg/ml.

A fourth liver biopsy at this time showed only a few persistent giant hepatocytes. Otherwise there was a striking restoration of liver architecture, with normal bile ducts and minimal residual portal fibrosis (Fig. 3).

The child, at two and one half years, is still on cholestyramine. Pruritus recurred when cholestyramine was decreased. Liver functions tests are normal; the serum bile acids remain slightly elevated (20 μg/ml).

Discussion

Cholestatic jaundice during the neonatal period is the result of diverse pathogenetic mechanisms. In some instances it occurs as a consequence of underlying hepatitis in the mother (2–4). In some instances it can be attributed to specific entities such as cytomegalic inclusion disease, toxoplasmosis, rubella, herpes simplex, cosackie B, as well as galactosemia, alpha-1 antitrypsin deficiency, hereditary fructosemia, tyrosinemia and cystic fibrosis (5–8). When such causes have been eliminated, however, one is still faced with a large nonclassified group, presumably of diverse origin, and also the possibility of extrahepatic biliary atresia due to choledocal cyst or extrahepatic biliary stenosis that may be surgically correctable (9).

Although there have been many attempts to distinguish between intrahepatic and extrahepatic causes of jaundice in infancy, there is no single test or procedure that can make the distinction unequivocally. In fact, in recent years the concept has been put forth that a common pathogenetic mechanism may exist which leads to intrahepatic cholestasis and varying degrees of biliary atresia (10). Patients, found at operation to have severe

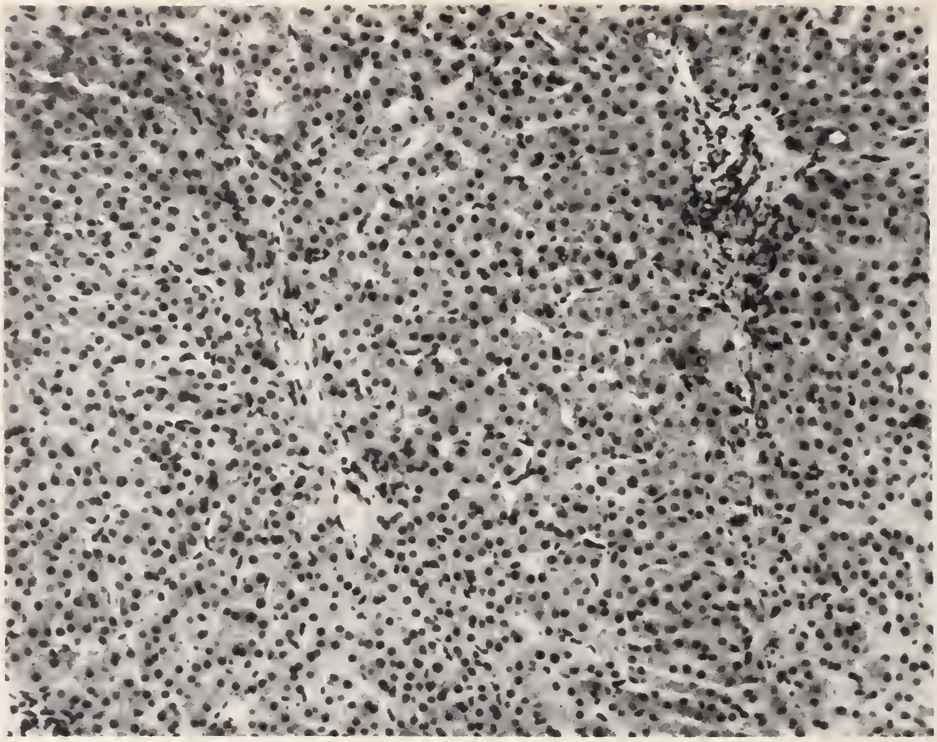

FIG. 3. Light micrograph of a representative field from the fourth liver biopsy. The portal tract is relatively inconspicuous due to reduction of inflammatory infiltration. Only delicate strands of fibrous tissue remain. The liver cell cords are somewhat irregular, but swelling and multinucleation have largely disappeared. The Kuppfer cells are less prominent than in the earlier biopsies. Hematoxylin and eosin stain. ×70.

intrahepatic cholestasis and patent bile ducts, may at autopsy have totally atretic ducts (11).

The causative role of bile acids in hepatocellular disease is increasingly being recognized (12–14). On the assumption that a reduction of bile acid concentration will remove one of the pathogenetic factors, it seems appropriate to use bile binding agents, such as cholestyramine, or a bile flow promoting agent such as phenobarbital, to produce a decrease in the intrahepatic level of these putative toxic substances (15, 16).

Although not universally accepted, biliary atresia is suggested by a predominance of chenodeoxycholic acid over cholic acid and by failure of cholestyramine to affect the ratio (17). When cholic acid is the main component of the circulating bile acid pool and cholestyramine causes a further increase in the ratio of cholic to chenodeoxycholic acid, neonatal hepatitis is likely.

Our patient illustrates several aspects of the differential diagnosis and therapy of neonatal cholestasis and jaundice. Although the initial Rose Bengal test suggested extrahepatic biliary atresia, liver biopsy was more consistent with neonatal hepatitis, as was the initial presence of urobilingen in the urine. Sequential liver biopsies showed progression of inflammation with advancing fibrosis. While liver morphology was deteriorating, his bile acid pattern was one of chenodeoxycholic acid predominance suggesting atresia. During cholestyramine treatment, this ratio diminished and was eventually reversed to one of cholic predominance. Concomitant with this biochemical change, not only did the clinical condition improve, but the liver architecture reverted to near normal.

It is of interest that liver function tests (SGOT, SGPT, bilirubin) were improving at a time when the liver pathology was progressing. The high serum bile acid levels correlated better with the pathologic findings.

Satisfactory results from the use of cholestyramine has been reported in a few patients with partial intrahepatic biliary atresia (18) and in patients with a paucity of bile ducts (19). Symptomatic relief of pruritus without amelioration of the basic disease has been reported by others in biliary cirrhosis (20).

From our experience it is suggested that bile acids may be the most valuable parameter to follow in the management of neonatal cholestasis. If early institution of therapy with agents such as cholestyramine and phenobarbital, are confirmed as being effective in preventing or reversing biliary stenosis and progressive hepatic fibrosis then it is hoped that in the future, every nursery wil have the capacity to screen newborns for cholestasis even before the appearance of jaundice, which may wel be a late manifestation of disease.

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Illness, Creativity and Marcel Proust

BERNARD STRAUS, M.D.

Creativity is a profound and baffling subject that is clouded in obscurity. It has been called the divine afflatus, a gift of the gods, inspiration, a perturbation of the spirit, and inspired madness. As an example, Edith Sitwell remarked of Blake that he was "cracked" but that was where the light came through! The bewildering complexity of creativity baffled Freud and makes definition or elucidation an enigma. For a long time, it has been thought by some that illness is a spur to creativity, especially to creativity in the arts. This idea has been encouraged by the fact that many invalids have contributed much to the world in enriching our understanding or adding beauty to our lives.

Many famous invalids come to mind. Proust and Darwin are outstanding examples. Sigmund Freud's long struggle with cancer did not halt his creativity. Florence Nightingale, Mary Baker Eddy and Joan of Arc had emotional illnesses. The great Spanish painter Francisco Goya suffered from physical and psychiatric disorders that were diagnosed as syphilis, neurolabyrinthitis, schizophrenia, psychotic depression, and involutional melancholia. He had recurrent attacks of partial paralysis, convulsions, impaired vision, hearing and speech, hallucinations and semicomatose states. It has been suggested that all of these may have been due to lead poisoning to which he was exposed in his work.

It was at one time believed that tuberculosis was a stimulus to creativity and the examples of Chopin, Schiller, Keats, Stephen Crane, Thomas Mann, Robert Louis Stevenson and Kafka come to mind. Distortions of body image occasioned by physical and other deformities have been cited such as those suffered by Byron, Walter Scott, and Talleyrand, all of whom had some form of lameness. Arnold Bennett's and Somerset Maugham's stuttering, Gogol's enormous nose, the impaired vision of Keppler, Bonnard, El Greco, James Joyce, James Thurber, Sean O'Casey, and Aldous Huxley have been cited in this respect. The war injuries of Hemingway, his insomnia, nightmares, and his father's suicide may have been factors in his creativity as well as in his own suicide.

Alphonse Daudet's chronic suffering, as a result of debilitating and painful illness, was described by Proust in a touching and poignant tribute, "Portrait of a Writer" (1). Here, he employs the recurrent image of the sick man lying in bed turning his face to the wall as a portent of death, as he later describes in *The Past Recaptured* and as Tolstoy did in *The Death of Ivan Ilyich* (2). Similarly, Cervantes' maimed left hand, Toulouse-Lautrec's spinal column disease (of which there has been much speculation in the medical literature), and Heine's paralysis have been considered to have had a significant impact on their work.

The number of homosexuals who have distinguished themselves is well known as is their prominence in the arts. Homosexuals have been fond of pointing to this fact as a suggestion that this form of sexuality is a feature of genius or inspires creativity.

Emotional illness has been called by Pickering the creative malady (3). Is psychopathology the source of art or the creative process in science? Many artists, writers and musicians have been notably afflicted with emotional illness. Scientists, on the other hand, who are also creative and in whom imagination is of an equal importance, have not been conspicuously neurotic–with a few outstanding exceptions like Darwin and some others. Is neuroticism the precondition for creativity? And if so, what mechanisms would explain the relationship? The role of the unconscious in creativity is undoubtedly of great importance. This is what we mean when we talk of inspiration, the afflatus, or the bolt from the blue. Proust's great emphasis on unconscious or involuntary memory as a stimulus to his creativity is important in this regard. It suggests the origins of insight that have been regarded as revelations or re-creations. He called it one of the two muses that inspired his work, the other being the nocturnal muse that referred to his dreams. Free association as evocations of memory and meaningful relationships must be regarded as part of the process of creativity. For Proust, creativity is a subjective process, a response to sensation, an affective experience.

Sensations such as those the narrator in *Remembrance of Things Past* experienced when he glimpsed the spires of Martinville, involuntary memories stimulated by the unevenness of the two steps when he visited the Guermantes' reminding him of the cobblestones of Venice, or the famous episode of the taste of the madeleine, resulted in a surge of creativity that led him to interpret the

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From the Department of Medicine, Beth Israel Medical Center, New York, N.Y. 10003.

sensations produced by these experiences as indications of fundamental laws and ideas. They impelled him to delve deeply into the obscurity of inchoate sensation to analyze what he felt and to convert it into a spiritual equivalent and a psychological tool for the understanding of creativity. He asks,

> "Now this method, which seemed to me the only one, what was it other than to create a work of art?"... "Those truths recorded with the aid of external objects the significance of which I sought to find within my head, where, jumbled together, steeples, wildflowers, they made up a complicated flower-be-decked medley, their first characteristic was that I was not free to choose them but they came to my mind pell mell. And I felt that that must be surely the hallmark of their genuineness. I had not set out to seek the two paving-stones in the court which I struck my foot against. But it was precisely the fortuitous, unavoidable way in which I had come upon the sensation that guaranteed the truth of the past which that sensation revived and of the mental images it released, since we feel its effort to come up into the light and also the thrill of recapturing reality. That sensation is the guarantee of the truth of the entire picture composed of contemporary impressions which the sensation brings in its brain, with that unerring proportion of light and shadow, emphasis and omission, remembrance and oblivion, which conscious memory and observation will never know.
>
> "To read a subjective book of these strange signs (signs standing out boldly, it seemed, which my conscious mind, as it explored my unconscious self, went searching for, stumbled against and passed around, like a diver groping his way), no one could help me with any rule for the reading of that book is a creative act in which no one can stand in our stead, or even collaborate with us."... "No matter what idea life may have implanted within us, its material representation, the outline of the impression it has made upon us is always the guarantee of its indispensable truth. The ideas formed by pure intellect have only a logical truth, a potential truth; the selection of them is an arbitrary act. The book written in symbolic characters not traced by us is our only book. Not that the ideas that we form ourselves may not be logically correct, but we do not know whether they are true. Only the subjective impressions, however inferior the material may seem to be and however improbable the outline, is a criterion of truth" (4).

In this section of the novel, Proust states his credo of art as a creative process. Sensations draw their sustenance from the very permanent essence of things. That essence is set free from its concealment and enables our true self, that had long seemed dead, to waken and take on fresh life. "A single minute released from the chronologic order of time has recreated in us the human being similarly released, in order that he may sense that minute" (5). For Proust, a sensation renewed takes on fresh life and releases us from the captivity of time in a manner not possible on the first experience of it. The experience, the kvale or feeling state or its evocation is all. It represents the flash of re-creativity that is the stuff of inspiration and is the characteristic of genius. Such a renewal is not simply a memory but rather a rebirth that enables us to savor life to its essence. And just as we rarely learn anything we did not know before, Proust suggests, in effect, we never truly experience the glory of a sensation that we did not feel before.

"The subjective impression is for the writer what experimentation is for the scientist, but with this difference, that with the scientist the work of the intelligence precedes, and with the writer it comes afterwards. Anything that we have not had to decipher and clarify by our own personal effort, anything that was clear before we intervened, is not our own. Nothing comes from ourselves but that which we draw out of the obscurity within us and which is unknown to others."

It is to concepts such as these that Greenacre refers in speaking of the artist's heightened perception of and increased sensitivity to the external world. An inborn reaction pattern of intensified awareness that not only permeates the artist's personal relationships in life, but also gives rise to the formation of collective alternatives such as nature, cosmos and universe, is of great importance to the creative mind.

The psychiatrist, William G. Niederland, has emphasized the presence of a permanent and often severe injury to infantile narcissism and its germinative effect on the creative potential (7). The narcissistic injury derives from early physical frailty or disability resulting from congenital malformations, bodily anomalies or protracted illness in childhood. Freud's own studies in this area have contributed greatly to our understanding of the dynamics of this injury. Proust's recurrent tragic refrain revolving about the transient deprivation of his mother's goodnight kiss in his childhood, represents a clear and severe insult to infantile narcissism to which he reverts time and again to the very end of his life. It is like the little musical phrase of the composer Vinteuil that Proust refers to again and again which is a leit-motif in *Remembrance of Things Past.*

The truly creative person whom we call genius is born, not made. He has a built-in endowment that may enable him at the age of three to play the piano or to compose an original composition, like Mozart, or like the great German mathematician Gauss, discover important algebraic laws at the age of nine. Yet the child prodigy in any field may fail to fulfill initial promise. Innate ability is a promise, not a fulfillment. Creativity requires certain conditions to develop, unfold and stimulate achievement. Illness may be such a stimulant, either by providing time and enforced leisure, or by the Teddy Roosevelt effect, – the drive to achieve as a compensation for infirmity. Wealth may be important by providing leisure. Chance, too, may be relevant by providing stimulation as a result of an encounter with an inspiring individual or by a felicitous choice of a career. The role of serendipidity in human development and discovery is abundantly documented.

Illness or defect may remain as an area of unresolved conflict through its concreteness, permanent narcissistic significance and resultant cathectic maldistribution. According to Niederland, "It strongly influences self-representation and the imaginative and symbolic processes, giving rise to a florid and secret fantasy-life. The permanent injury attaches itself to the subject's inner world of self-representations and object-representations, and it tends to intensify personal tensions and the familiar conflictual anxieties–castration fear, aggression, vengefulness, and lifelong rancor—from early life to the point of massive influence on character formation and ego-superego development."(8) In gifted persons, the urge toward body reparation is said to frequently take the path of creative restitution.

Object loss and grief are of great importance in relation to the creative efforts of Proust. After several abortive efforts, he began work seriously on *Remembrance of Things Past* in 1909, only after the death of his mother. His father had died only two years before. Psychoanalytic theory suggests that the child identifies those close to him, especially parents, with his own body image. Thus, such an object loss represents a threat to one's body image and even to one's existence. Identification of diseases of the parents or a sibling with the self is common in all people. The medical student frequently identifies with the diseases of his patients and often fears that he has the same manifestations or symptoms of the patients he examines, or of the disease he studies.

Such an identification may be extended to people, places, and even to objects. It is not too fanciful to say that writing or art may represent an effort to restore the loss of one's past existence or being. Thus, Proust's writing may be viewed as having been stimulated by a need to restore the object loss represented by the death of his parents and to return, not to the womb, but to a previous period in his life. His writing was autobiographical to an even greater degree than most imaginative writing. Certainly autobiographical writing may properly be viewed as narcissistic. It is restitution of what has been lost and, indeed, loss is the principal theme of Proust's novel. It is not only time that has been lost, it is nnocence and illusion; it is parents, friends, and lovers.

The quest of the novel is to imprison them as Albertine was imprisoned; to recapture all those things that represent Proust's life and being, and to fix them forever in his book since he could not keep them in his life. Thus, writing and other forms of art may be viewed as recreation or restoration. Nostalgia removes the odious or banal present, and the fearsome future with its awesome surety of death brought vividly to the level of reality by the object loss. Writing represents capture of existence, of time, of those we love even after they have died.

The memory of an experience or of a love object is as close as we can come to regaining the reality of a part of ourselves. Losses of parts of ourselves–people, places or things, necessitate mourning, memorializing or remembering. This expression or catharsis mitigates the anguish and makes it more endurable. Death and other loss is a threat that leads to depression and Proust was so depressed about the death of his mother that for some months he could write nothing. After overcoming the shock of his initial grief, he returned to his writing in dedicated seclusion and did not stop writing until his death. His writing fulfilled the restorative need for object loss or re-creation of the past and its preservation.

The death of his parents also enabled him to write more freely concerning those sexual deviations and aberations such as his sadomasochism, homosexuality, and lesbianism that were such important parts of his concerns of life and, of course, would have shocked his family greatly. So strong was his superego and this protective instinct that, even after the death of his parents, he was compelled to transform his male lovers to female representations. He does it so effectively that Edmund Wilson is moved to express doubt that such a transposition was actually performed.

Proust could expose his soul but not his practices. The moral climate of his time made the invert so great an object of revulsion that Proust could not identify himself as an invert. His ambivalence, moreover, was such that he at times could write with great sympathy and understanding of homosexuality and at other times with comic cruelty. It is possible also that exposition represented expiation. His writing was a fulfillment of his family's, especially his mother's, hopes, aspirations and expectations that he would write an important work. It represented a mitigation of his guilt feelings occasioned by the belief that he had failed them by his idleness, his abnormalities and his lack of achievement. Like most people but to a greater degree, Proust had an intense need to leave something of himself behind. What better way was there to do this than by an achievement in an area, Art, that to him represented the highest form of man's accomplishment?

Also, since the worsening of his asthma and his hypochondriasis was accompanied for a dozen years before his death by a fear of imminent death, his drive arousal was heightened by a compulsion to complete his work before he died. It is not surprising that living with illness leads to thoughts of and preoccupation with death. The idea of loss of self in a narcissistic individual stimulates a talented person to creativity. It is of course possible that the stimulus may not result in the realization. Desire may outrun performance. Neurotic aspiration without ability may result in frustration, despair, and even suicide. Inner conflicts and emotional perturbations may overwhelm the psyche and result in paralysis of performance. A masterwork requires the soil, the preparation, and the drive or cathectic capability for its realization.

Suffering and the idea of death are potent stimuli to creativity but probably not the only ones. For Thomas Mann, they represented the path of genius that leads through the valley of death. Others, like Bach, were preoccupied with thoughts of death. Suffering is a predominant theme of Somerset Maughan's greatest novel, the autobiographical *Of Human Bondage*. But some may not require so potent a stimulus to release their creative impulses or capacities.

Other factors were present in Proust than those representing object loss. He had a need to dissect, to analyze and to understand. Proust had a philosophic bent and needed to distinguish between the antinomies of illusion and disillusion. He had a fertile mind and imagination that resulted in a streaming of images and ideas that he knew were worth recording. He had the awareness or consciousness of talent and selfworth. He knew he could write and, in so doing, could achieve selffulfillment. Proust needed more than most the admiration and praise that give sustenance to the insecure and that comes with successful achievement. His productivity became the fulfillment of his rapacious ego. He had original ideas on love, time, illness and death that he wanted to try out on the world and was then intent on listening for the echo.

Proust had overflowing reserviors of repression and aggression. In Jung's formulation, his persona was that of an ingratiating, humble, weak and dependent individual; his anima was a truer representation of the man and reflected a sharp, dissecting, analytical and critical mind. He needed to discharge his pent-up stores of aggression and did so sometimes by exercising his talent for ridicule and mimicry, in his life and in his writing.

Writing enabled Proust to reduce a disorderly succession of images, inner processes, conflicting ideas, wild imaginings, and unreasoning fears, rages and anxieties, to coherence, proportion and order. It made possible the single-minded pursuit of relevance from the disappointing reality of experience and the chaotic surge of fancy and emotion to which his heightened sensitivity and sensibility made him vulnerable. It was this devotion to selfrealization and understanding that led to his dedication to his work, his creativity stimulation and to his becoming a recluse. The fact that he became a recluse aided his creativity but did not inspire it.

Freud, who had striking powers of analysis and imagination, was similarly driven, as Philip Rahv says in his essay on "Freud and the Literary Mind," by an indomitable search for empirical knowledge that also exceeded the confines of scientific inquiry in its narrow sense (9). Freud had a close affinity to the literary mind and though he does not seem to have known Proust's work, frequently paid tribute to the contributions of literature made by poets and writers, modestly saying, "In psychological insights . . .they are far ahead of us ordinary people because they draw from sources that are not yet accessible to science."

To these few is given the ability "to salvage from the whirlpool of their emotions, the deepest truths to which we others have to force our way, ceaselessly groping among torturing uncertainties."

It is clear that Freud's gifts included literary ones as Proust's included psychological understanding. The linkage between literature and psychology is not necessarily that writers or poets suffer from emotional illness but that they deal with psychological mechanisms whether formally defined or intuitively acquired.

Infirmity of Mind

Both Proust and the narrator in *Remembrance of Things Past* are constantly engaged in agonies of introspection and reappraisal. Prominent is a dissatisfaction with self that leads to coloring people and objects with a roseate hue of illusion, leading inevitably to disappointment and disillusionment. There is constant seeking for the ideal, but like all of us, Proust' reach is beyond his grasp. The circumstance of possession itself leads to deprecation and diminution. We recognize in Proust, as he does in the narrator, our own frailties that some have learned to accept but with which he cannot cope.

Proust's infirmities are human, only more so. He feels more keenly than the rest of us. His is a spiritual disease. There is always striving or yearning for the realization of something he does not possess but knows is very desirable. His disease is excess. His neurosis is an excess of sensibility or of selfdoubt. It is exaggeration almost to the point of disease. We recognize in Proust all the foibles of our humanity in superabundance and it is this finely honed exaggeration, this larger than life quality, that brings recognition of truth because it makes it more readily discernible.

Proust may be said to be an ultrarefined representation of all mankind, with selfawareness and an ability to articulate that awareness. It is not so much that the essential Proust is flawed, it is that he is extreme–in his relationships, in his unhappiness, in his selfdoubt, and in his insecurities. This is his neurosis of which narcissism is one expression. He worries himself and others almost to distraction. In his view, everything becomes flawed.

All his friends, finally, are flawed by triviality or vulgarity, inversion or perversion, by homosexuality or sadomasochism, just as Proust himself is so flawed.

Everything becomes tawdry and loses it glow. In a way, he is a child who invests everything with a wondrous glamour and an impossible idealism and then is depressed and dejected when truth breaks in with all her matter-of-fact and coarse reality. It is this that we mean when we talk about Proust's sensibility. Proust is also very susceptible; he is ultrasensitive. He is impressionable.

We must define what is meant by these characterizations. Sensitivity is the capacity to respond or be affected by something. Susceptibility is the state or quality of being impressionable and responsive, especially to emotional stimuli. Sensibility is, particularly, a capacity to respond to esthetic and emotional stimuli, delicacy of emotional or intellectual perception. These of course are related qualities. They are the qualities of the artist who feels and receives sensations either more acutely than others, or with the same perceptions but with the ability to articulate them, to express them in words, pictures or sounds.

We are affected by Proust's complaint because we have all been touched by it. For better or worse, most of us have accommodated to the loss of illusion, or have made our peace and adjusted to it or accepted reality. Proust cannot, and hence, is neurotic and unhappy. The complaint of some has been that psychiatrists seek to adjust us into obtundity or an acceptance of things as they are, to transform our rebellion into conformity with the establishment, and to shrink us into the real world from the world of idealism, hope, aspiration and illusion. In this sense, adjustment is a contraction and the popular term "shrink" as a synonym for psychiatrists is suggestive of reduction and diminution.

It is Proust's refusal to accept diminution which leads to his search, the *recherche*. At his birth, he was at first thought to be too weak to survive. As a very young child, Proust was regarded as "delicate." This would appear to refer not only to his physical health but to his gentle and sensitive nature. He was greatly adored by his mother and grandmother, who lavished so much affection on him that he became extremely dependent on them.

His chief physical illness, bronchial asthma, came later at the age of nine. His dependency and insecurity, however, preceded the onset of his asthma. At the age of thirteen, he could say in reference to the question, "What do you regard as the lowest depth of misery?" "To be separated from Mama." This excessive dependence may have been a reflection of his parents' concern for his survival as an infant and the constant overanxiety and solicitude they lavished on their first-born. The human infant is, of course, incapable of an independent existence; but his weakness and helplessness may be prolonged and exacerbated by parental attitudes. According to Alfred Adler, this leads to feelings of inferiority that become a driving force that demands not only security, peace, social equilibrium and acceptance, but also a striving to express power over the environment, a goal of dominance over one's fellows (10).

Children who have such a goal, Adler says, are always easily recognized. They become "problem children" because they interpret every experience as a defect and because they consider themselves always neglected and discriminated against both by nature and by man. With the onset of Proust's bronchial asthma, such ideas were undoubtedly given added credence and credibility.

A child who grows up in such an adult environment is predisposed to consider himself as Proust did, as weak, small and incapable of living alone in an independent existence; he does not trust himself to do those simple tasks that one thinks him capable of doing, without mistakes or clumsiness. And indeed Proust, even as an adult, felt compelled to call upon his family and friends for help and moral support in making the simplest and most mundance decisions.

Adler says that some children are regarded as valuable property that must be carefully watched while others are made to feel that they are so much useless freight. A combination of such attitudes on the part of the parents and the adults often leads a child to believe that there are but two things in his power, the pleasure or displeasure of his elders. Proust sought the acceptance and approval of others all his life by an excessive generosity and an ingratiating manner. This may be a reflection of overindulgence by parents, that often has an element of ridicule, condescension and tacit rebuke.

Such attitudes, Adler says with some heat, are well-nigh criminal. They retain their effect upon the soul of the child and are transferred into the habits and actions of his adulthood. This leads to that "infirmity of nature" which Shattuck quotes from Montaigne as "soul error" (*une erreur d'ame*). It is this infirmity of his nature that led to a constant striving to compensate for and to achieve recognition and superiority. It also resulted in the devaluation and transformation of the gold of his aspiration into the dross of its realization. So profound were his feelings of inadequacy and insecurity that the very fact of success was a signal of failure since his weakness and lack of feelings of self-worth made success impossible for him.

Proust's episodes of hysterical weeping were cries of anguish for lost illusion, and also for feelings of frustration and inadequacy. As Shattuck says, Proust's complaint was his error of soul that rendered him incapable of giving full value or status to his own life and experience. It was his frailty of body and of mind that posed a formidable barrier to acceptance of selfworth and achievement. Thus, both nature and nurture conspired to foster his neurotic needs and make him dependent and weak. They may also have provided the driving force that enabled the realization of his creativity and his genius.

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Leiomyosarcoma of the Superficial Soft Tissues

LESTER ROSEN, M.D., BENJAMIN A. PAYSON, M.D., and KEN MORI, M.D.

Introduction

Leiomyosarcoma of the superficial soft tissue is considered to be a rare tumor. However, the literature suggests that they are not uncommon: at least 104 cases have been reported; 33 cases were cutaneous, and 71 in the subcutaneous tissues (1–12). Clinically, the lesion is usually benign in appearance and awareness of its existence is prerequesite to proper initial management. This report includes a description of two additional cases, review of the literature, and discussion of management.

Case Report

Case 1: A 29-year-old white male had a mass in the left posterior triangle of the neck in 1978. The mass had been present for one year. The mass which measures 4 × 4 cm, was painless, firm and fixed to the skin, but moveable against the underlying tissue. There was no associated adenopathy. The tumor was locally excised with a section of attached skin. After the diagnosis was confirmed, a wide excision of the previously operated site with application of the split thickness skin graft was performed. One year later, the patient is well with no evidence of local recurrence or metastasis.

Grossly, the tumor was an ovoid, well demarcated nodule measuring 3.5 × 3 × 2.5 cm. The cut surface revealed grey-white whorls. (Fig. 1). Microscopically, the tumor consisted of interlacing bundles of spindle-shaped cells. The nuclei were elongated and the nucleoli were prominent and blunt ended. Mitoses was seen as frequently as two per high power field. Collagen was sparse (Fig. 2). In one area, the tumor invaded the adjacent adipose tissue. The diagnosis was leiomyosarcoma.

Case 2: A 40-year-old Russian female was admitted with a painful mass on the lateral aspect of her left knee in 1978. This mass had been observed in 1967 in Russia at which time local excision was performed. The tumor recurred in 1971, 1974 and 1976 and each time local excision was performed. On admission to Beth Israel Medical Center, there were no palpable lymph nodes and the physical examination was within normal limits. After an initial incisional biopsy confirmed leiomyosarcoma, the patient underwent wide excision with split thickness skin graft. Ten months after the operation, the patient is well, with no evidence of local recurrence or metastasis.

A firm, well demarcated mass measuring 1.5 × 1.5 × 1 cm was attached to an elliptical segment of skin measuring 10 × 8 cm. Two healed linear scars were noted on the skin. A segment of muscular tendon was observed on the under surface of the specimen. The cut surface of the mass revealed two grey-white whorls. Microscopic examination showed subcutaneous proliferation of elongated cells with blunt-ended nuclei arranged in interlacing cords. Mitoses averaged two per high power field.

Electron microscopy revealed that the tumor was fairly uniform and consisted of irregular cells with irregular, sometimes serrated, nuclei. The cytoplasm revealed numerous slender uniform filaments, dense bodies, and zones of glycogen particles. The cells interdigitated and were attached to one another by desmosome-like structures. Extracellular collagen was extremely sparse (Fig. 3). The diagnosis was recurrent leiomyosarcoma.

Discussion

Leiomyosarcoma is a malignant smooth muscle neoplasm and may develop in any part of the body. Better known varieties of this malignancy are those originating from organs with abundant smooth muscle such as the uterus and gastrointestinal tract. The skin and subcutaneous tissue contain smooth muscle in the arrectores pilorum, tunica dartos, erector muscle of the nipple, and the media of blood vessels. These structures are the infrequent sites of soft tissue leiomyosarcoma (1). The biological behavior of the tumors at these infrequent sites is similar to those found at the more common

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From the Departments of Surgery and Pathology, Beth Israel Medical Center, New York, N.Y. 10003.

Requests for reprints should be sent to Lester Rosen, M.D., Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York City, N.Y. 10003

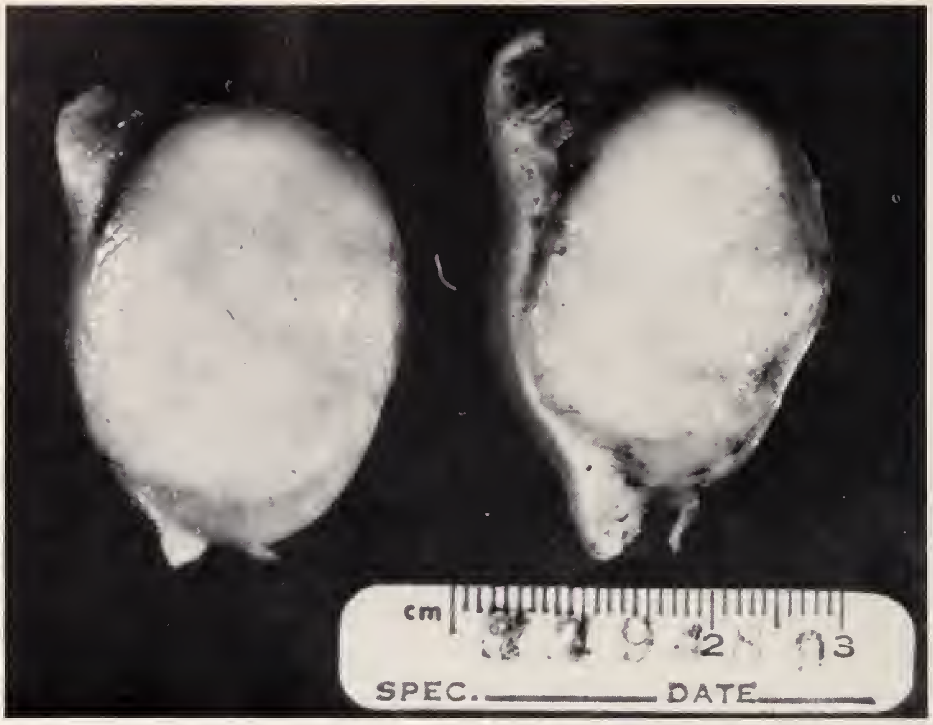

FIG. 1: Cut surface of leiomyosarcoma (Case 1). Note demarcation and attachment of the tumor to the skin.

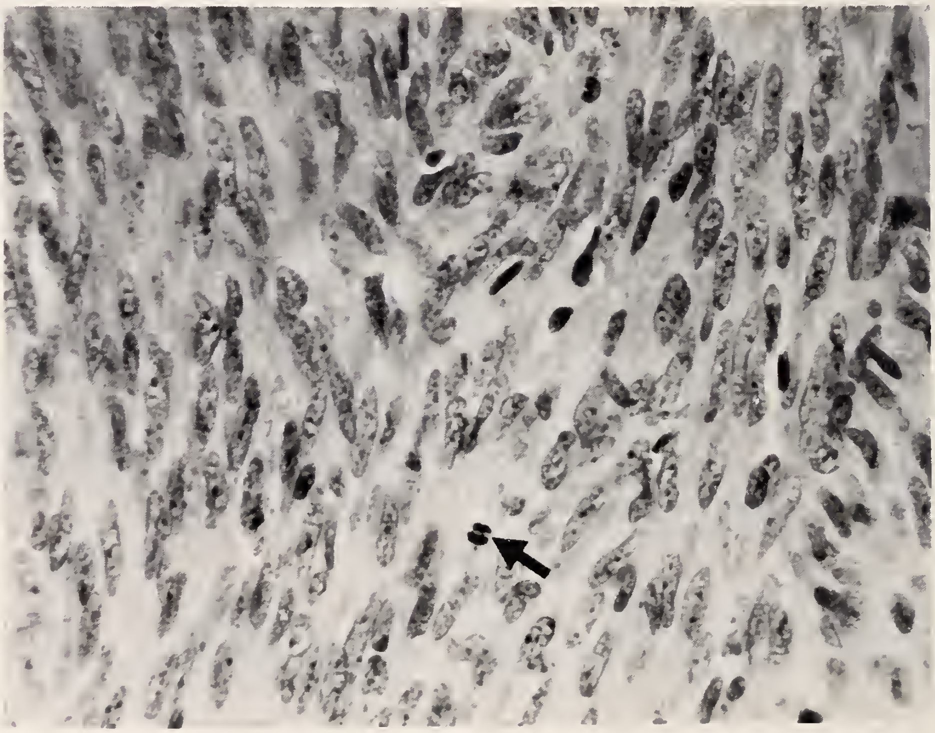

FIG. 2: Histology of leiomyosarcoma (Case 1). Note streaming pattern of elongated nuclei and a mitosis in anaphase (arrow). Hematoxylin an eosin. (X380)

locations, in that they spread predominantly via the hematogenous route and uncommonly via lymphatics (2, 3).

The histologic criteria of malignancy is based primarily upon the frequency of mitoses (13). In one of the largest series of soft tissue leiomyosarcomas, Stout and Hi examined 35 cases and stated "if mitoses can be found average rate of 1 or more in every 5 high power field the tumor is almost certainly malignant, and if the m toses are as frequent as 1 or more in every high pow

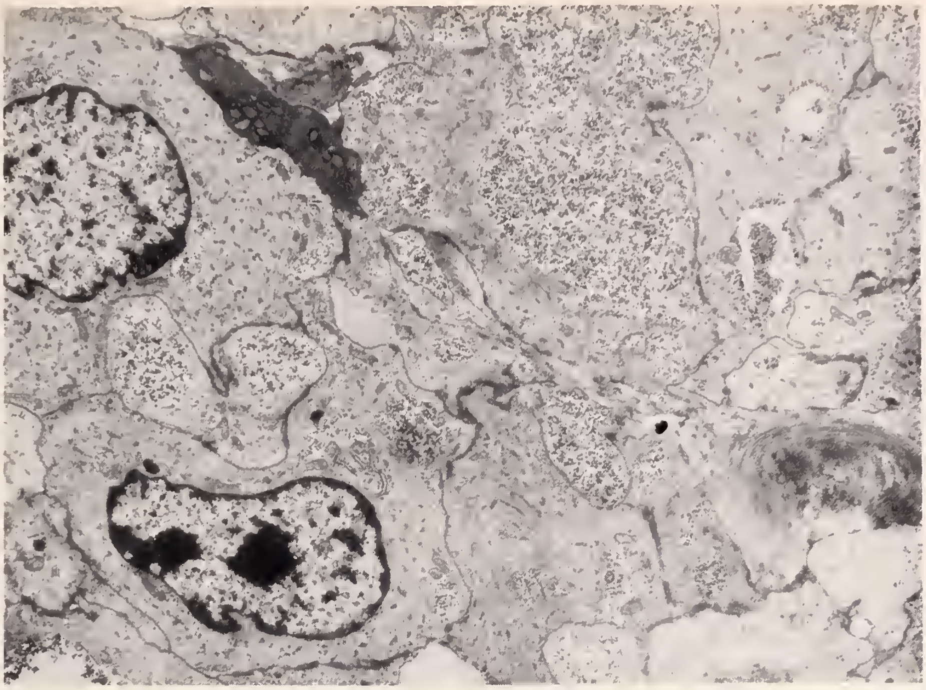

FIG. 3: Electron microscopy of leiomyosarcoma (Case 2). Note interdigitation with desmosome like structures, irregular nuclei, and cytoplasm with fine filaments, dense bodies and zones of glycogen particles. (X4500)

field, the tumor is certainly malignant"(4). Histology of the two cases described herein amply satisfies this criterion. In the same article, they also made the following observations. Leiomyosarcoma is usually painless in contrast to leiomyoma, of which 80% are painful. The most common location is in the lower extremity and they occur at any age with equal propensity for both sexes. Tumors larger than 2.5 cm are more likely to be sarcoma. Seventy-two percent of 36 cases either locally recurred, metastasized or both. Recurring tumors are larger and are fixed to the contiguous soft tissue structure.

Frozen section examination of the tumor at the time of initial operation is of questionable value. Since the frequency of mitoses is the important histologic criterion of malignancy, frozen section would necessitate multiple tissue sampling that is not only impractical but may contribute to extensive tissue artifact in permanent histologic sections. If the tumor is large, an incisional biopsy for frozen section may be taken with the understanding that the diagnosis would not be definitive but suggestive of sarcoma. Fortner advocates that the skin incision for biopsy should be compatible with later radical excision and that absolute hemostasis and closure of the biopsy site in layers without drainage are imperative (14).

With or without frozen section examination, initial excision should include a generous amount of the grossly uninvolved tissue around the tumor. With definitive diagnosis of leiomyosarcoma in permanent histologic sections, wide resection of the tumor site is mandatory. Four local recurrences over the period of ten years in the second patient attest to this. The extent of resection is determined by the location, the size and characteristics of the tumor. In our cases, an intact normal muscle or fascial barrier between the tumor and margin of resection was present. Some advocate excision to the origin and insertion of involved muscle as these tumors may extend along muscle bundles, nerve sheaths, and fascial planes (4). Prophylactic lymph node dissection is not indicated. However, if the tumor and adjacent lymph nodes can be excised in continuity, this may be the procedure of choice (5). Rising and Booth advocated radical neck dissection for recurrent nodules of the neck (2). The solitary pulmonary metastasis can be resected by thoracotomy (6). No specific chemotherapeutic agent is available at present.

Summary

Prerequisite to successful management is awareness of the malignant potential of any solid tumor in the superficial region. Unlike the deep seated or visceral varieties, leiomyosarcoma of the skin and superficial tissue can be recognized early and treated promptly with expectation of an excellent prognosis.

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Immunoperoxidase Localization of Carcinoembryonic Antigen in Benign and Malignant Colorectal Tumors and Related Mucosa

RICHARD J. STENGER, M.D., ADA B. CHABON, M.D., F. JAMES PRIMUS, PH.D.*, AND WILLIAM I. WOLFF, M.D.

Introduction

Carcinoembryonic antigen (CEA) has been identified as a glycoprotein present in fetal gut and in many neoplasms, especially those of the gastrointestinal tract (1–6). As a circulating antigen, CEA is also found in the plasma or serum of patients afflicted with various tumors (7–13). Many investigators have localized CEA to tissues suspected of producing this substance, but there has been a lack of uniformity concerning the details of such localization. (14–30) This variability has been particularly evident in reported studies of colorectal polyps (5, 14, 15, 25, 28, 29). Accordingly, the following investigation was undertaken to determine the locus and extent of CEA staining in colorectal neoplasms, both benign and malignant. Staining in the carcinomas was also compared with the reaction in mucosal samples, proximal and distal to the primary cancer.

Materials and Methods

The study included 58 polyps resected via a flexible iberoptic colonoscope and 13 carcinomas obtained as urgically resected specimens. (31) The polyps came from various levels in the large bowel with the lowest 8 cm nd the highest 130 cm above the anus. Sixteen of the 58 umors were more than 50 cm beyond the anus. The polyps ranged from 1.0 to 7.0 cm, with 22 of them exceeding 2.0 cm in diameter. Tumors less than 1.0 cm in iameter were excluded from this study. Twenty-seven of the polyps were lobulated, the remainder being smooth-surfaced. Microscopically, 22 were categorized as tubular adenomas (adenomatous polyps), 33 as villotubular (mixed) adenomas, and three as villous adenomas.

Of the 13 malignant neoplasms, three were in the cecum, one in the ascending colon, one in the transverse colon, one in the descending colon, five in the sigmoid, and two in the rectum. Tumor size ranged from 1.5 cm to 7.0 cm. Six of the neoplasms were annular, constricting lesions; seven were exophytic and coarsely lobulated; all showed at least some surface ulceration. Microscopically all were adenocarcinomas, one poorly differentiated, one well differentiated, and the rest, moderately well differentiated. Of the 13 cancers, one was classified as Duke's A, five as Duke's B, and seven as Duke's C. In ten of the cases, the proximal line of resection was less than 10 cm from grossly visible neoplasm, but in one instance the proximal margin was 68 cm from visible tumor. In nine of the 13, the distal line of resection was less than 10 cm beyond the primary, but in one instance the resection margin was 12 cm distal to the carcinoma. In no instance was a resection margin either grossly or microscopically involved by the malignancy.

For CEA detection, comparable fresh-frozen and formalin-fixed, paraffin-embedded sections were made from each tumor, whether benign or malignant; and, in each case, conventional hematoxylin and eosin-stained sections paralleled those chosen for CEA staining. The resection margin samples from the surgical specimens were handled in a similar manner.

Tissue localization of CEA was achieved by a previously reported three-step, unlabelled antibody, immunoperoxidase technique (26). After absorption of the goat CEA antiserum with a mixture of major blood group erythrocytes, antibody crossreactive with colon carcinoma antigen-III (CCA-III) was removed by absorption onto a CCA-III-containing immunoadsorbent (32). Specificity of the staining reactions was confirmed by dupli-

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From the Departments of Pathology and Surgery, Beth Israel Medical Center and Mount Sinai School of Medicine of The City University f New York, N. Y.; and the Department of Immunology, Hoffman-La oche, Inc., Nutley, New Jersey.

* Present address: Division of Experimental Pathology, University Kentucky Medical Center, Lexington, Kentucky 40506.

Requests for reprints should be sent to: Richard J. Stenger, M.D., epartment of Pathology, Beth Israel Medical Center, 10 Nathan D. erlman Place, New York, N.Y. 10003.

cate, control sections treated with anti-CEA serum freed from CEA antibody by adsorption onto a CEA-containing immunoadsorbent. For the anti-CEA serum, rabbit anti-goat IgG serum, and goat antiperoxidase serum, dilutions yielding optimal staining reactions had been predetermined to be 1:300, 1:50, and 1:100 respectively. The extent and characteristics of endogenous peroxidase activity were judged from sections treated only with diaminobenzidine and H_2O_2.

Results

Fresh-Frozen Tissue: With fresh-frozen sections, the three-step immunoperoxidase technique employed in this study detected CEA-specific staining in all of the colorectal tumors although some stained more intensely than others (Table I). Moreover, in the malignant cases, the resection margins also displayed CEA-specific staining when fresh-frozen sections were used, again with some variation in intensity (Table I). Only the fresh-frozen, control sections were completely negative for CEA-specific staining.

CEA staining of the benign tumors, as shown in Figures 1 and 2, showed no differences that could be correlated with location in the bowel, polyp size, or gross surface characteristics; nor were there any consistent differences among the various histologic categories (Table I). Thus, of 22 tubular adenomas, 18 were intensely stained for CEA, as were 24 of the 33 villotubular polyps (Fig. 2) and all of the villous adenomas (Fig. 1).

Twelve of the 13 colorectal adenocarcinomas were strongly positive, but this CEA-specific staining did not notably vary with location in the bowel, tumor size, gross or microscopic features, or the Duke's classification. In nine of the surgical specimens, the proximal resection margin stained as intensely as the primary tumor, including the one instance in which this margin was 68 cm proximal to grossly visible neoplasm. (Table I). In 11 of the specimens, the distal resection margin was also strongly positive, including the case in which the CEA-stained margin was 12 cm beyond the carcinoma.

In the fresh-frozen sections, whether from benign or malignant tumors, the CEA-specific staining appeared as a sharp, linear precipitate localized to the region of the glycocalyx along the luminal aspect of the epithelial cells (Figs. 1 and 2). Frequently a discrete, finely granular stain was also noted in the apical cytoplasm of such cells (Fig. 2). Similar staining patterns were evident at the resection margins.

Formalin-Fixed, Paraffin-Embedded Tissues: Formalin-fixed, paraffin-embedded tissues invariably revealed a less intense CEA-specific stain than was evident in the parallel fresh-frozen sections (Fig. 3) (Table I). In addition, staining of the fixed material was more diffuse less sharply localized, and never discretely granular (Fig 3). Still, most of the tumors, whether benign or malignant, showed CEA-specific staining; however, those tha were less intense in the fresh-frozen preparations were usually negative in the formalin-fixed, paraffin-embedded counterparts (Table I). Moreover, mucosal staining a the resection margins of the surgical specimens was les definitive in the formalin-fixed, paraffin-embedded material.

Discussion

With fresh-frozen sections, CEA-specific staining wa evident in all of the colorectal tumors tested by the three step, unlabelled antibody, immunoperoxidase techniqu used in this study. There were some variations in stainin intensity, but both benign and malignant neoplasms frequently showed a marked CEA reaction (Table I). Th staining variations could not be correlated with eithe gross or microscopic differences in the tumors. Thes observations are in accord with previously reported in

TABLE I

Assessment of CEA-Specific Staining in Colorectal Tumors and Related Mucosa

Specimen categories	Number of specimens tested	staining intensity of sections from fresh-frozen tissue			staining intensity of sections from formalin-fixed, paraffin-embedded tissue		
		Intense	Moderate	Absent	Intense	Moderate	Absent
Tubular adenoma	22	18	4	0	0	16	6
Villotubular adenoma	33	24	9	0	0	19	14
Villous adenoma	3	3	0	0	0	2	1
Adenocarcinoma	13	12	1	0	0	9	4
Proximal resection margin	13	9	3	1	0	5	8
Distal resection margin	13	11	2	0	0	8	5

Histologic sections were made from fresh-frozen and from formalin-fixed, paraffin-embedded tissue samples of each specimen. A three-ste unlabelled antibody immunoperoxidase technique was used, with suitable controls, to detect CEA-specific staining in both fresh and fixed tiss sections.

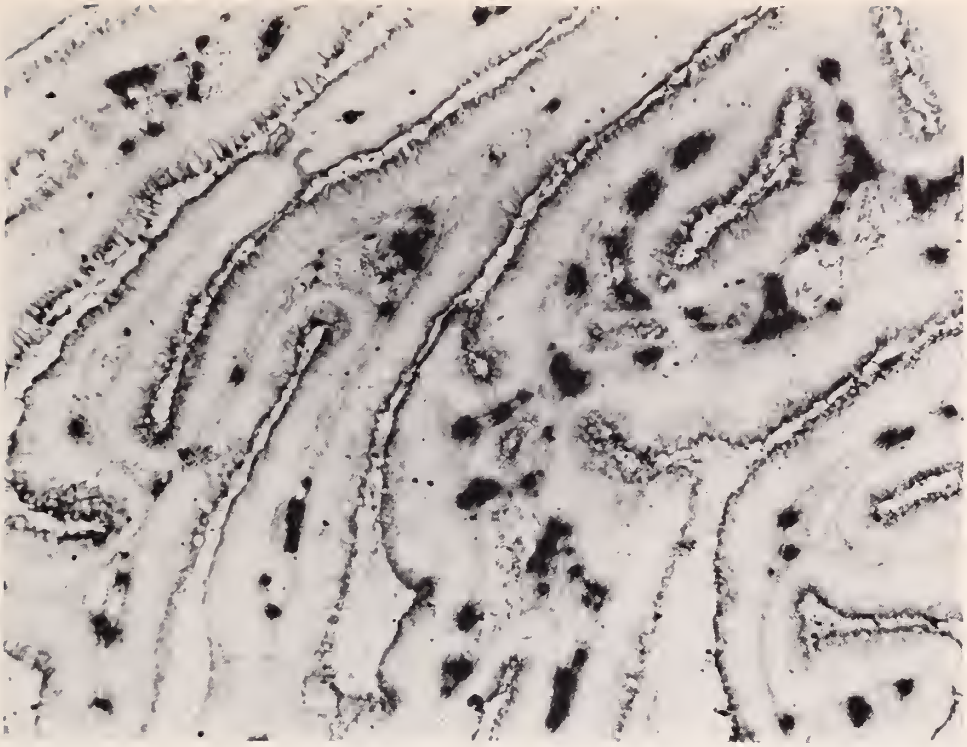

FIG. 1. Fresh-frozen section from a portion of a villous adenoma. The micrograph displays the CEA-specific stain as a sharp, linear density xtending along the luminal aspect of the epithelial cells lining the fronds of the tumor. The irregular, dark blotches within the stroma of the ronds represent endogenous peroxidase activity of leukocytes and erythrocytes. CEA immunoperoxidase stain. (X80.)

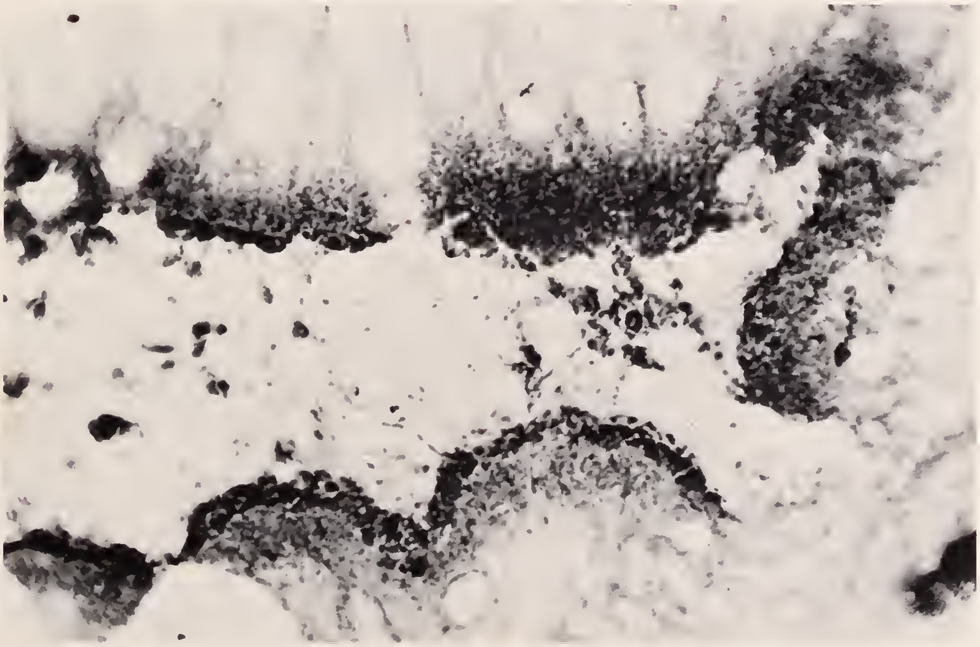

FIG. 2. Fresh-frozen section revealing a gland in a villotubular adenoma. The CEA-specific stain, not only closely follows the luminal aspect of he epithelial cells lining the gland, but also appears as discrete, black granules within the apical cytoplasm of these cells. In addition, a small mount of positively stained material is present in the lumen of the neoplastic gland. CEA immunoperoxidase stain. (X 1,000.)

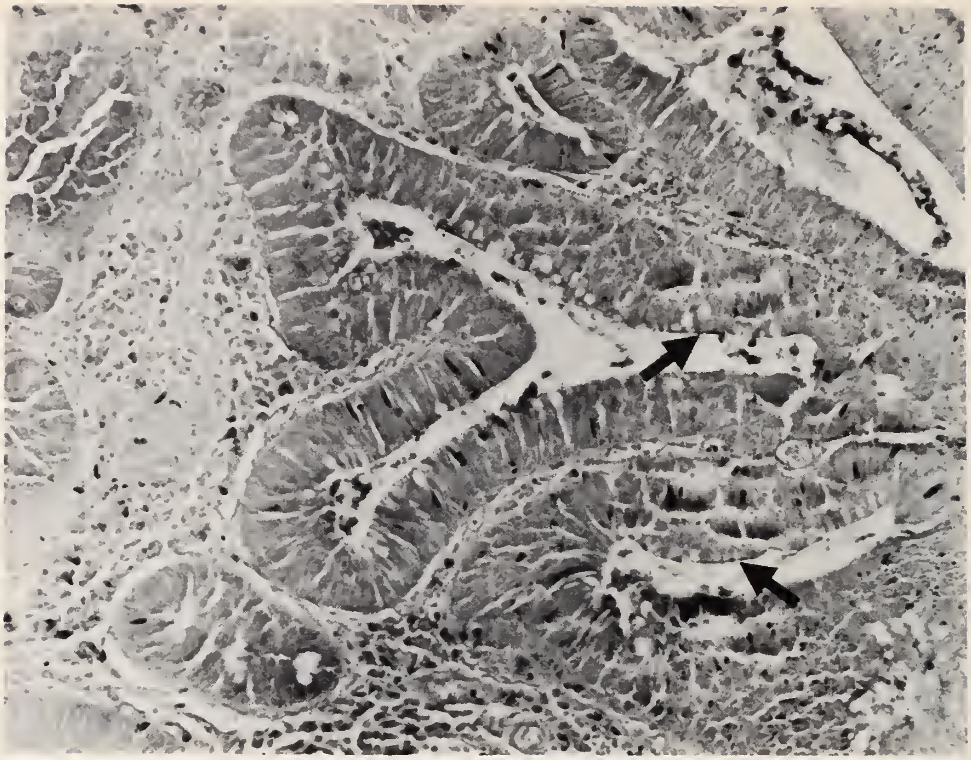

FIG. 3. Formalin-fixed, paraffin-embedded section depicting glands in a villotubular adenoma. CEA-specific stain is seen as a moderately dense incomplete, thin line extending along the apical aspect of the epithelial cells lining the glandular structures (as at arrows). Much of the stain however, appears as a diffuse, faint discoloration spread throughout the cytoplasm. CEA immunoperoxidase stain. (X 125.)

munofluorescent studies and with quantitative biochemical analyses indicating that the CEA content of colonic polyps is comparable to that of colonic carcinomas (5, 14, 15, 17, 29, 30).

Some investigators, however, have not detected CEA-specific staining in benign colonic polyps with immunoperoxidase techniques (21, 25). This failure might be explained by technical factors related to the test, but our observations and the recent results of Sharkey et al would seem to indicate that formalin fixation interferes with optimal tissue retention of CEA-stainable material, particularly if such fixation is delayed or the tissue has aged in the paraffin block (5, 25).

Previous studies have localized CEA to the apical pole of neoplastic epithelial cells or along their luminal surface as well as within the glandular lumina (14–18, 20, 21, 23, 26). Investigators using fresh-frozen tissues have generally localized CEA to the glycocalyx and subjacent cytoplasm where we also detected the CEA-specific staining (Fig. 2) (16, 19, 23, 27, 30). Such localization is consonant with the concept of CEA packaging and distribution to the surface from cellular sites of manufacture via a lysosomal mechanism (16, 19, 23). This concept requires verification, but the importance of using absolutely fresh tissue for such studies seems apparent.

Noteworthy in our study was the frequent occurrence of relatively intense, CEA-specific staining of the epithelium at the resection margins of the surgically extirpated malignant bowel tumors (Table I). The presence of CEA in mucosa adjacent to colonic tumors has been previousl noted and has been ascribed to CEA shed from th primary neoplasm (5, 15, 21, 22, 29). In one of the case reported here, however, mucosa 68 cm proximal to th primary malignancy was strongly positive for CEA. It i difficult to explain this as a "backwash" phenomenon o bathing of the mucosa by CEA released into the intestina lumen from the primary tumor. The explanation of suc staining awaits elucidation.

Summary

Carcinoembryonic antigen (CEA) was detected by three-step, unlabelled antibody, immunoperoxidase technique in 58 endoscopically resected colorectal adenoma and 13 surgically extirpated colorectal adenocarcinoma In fresh-frozen sections, all of the benign and malignan tumors showed CEA-specific staining, often rathe intense and generally seen as a linear density alon the luminal aspect of the epithelial cells and as discrete granular material within their apical cytoplasm Formalin-fixed, paraffin-embedded tissues invariabl showed a less intense CEA stain than was evident in th parallel, fresh-frozen sections from the same specime This immumoperoxidase technique did not discriminat among various gross and microscopic features of th

colorectal tumors. Notable, however, was the frequent occurrence of relatively intense, CEA-specific staining of the mucosa at the resection margins of the surgically extirpated neoplasms.

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Uterine Packing: A Reappraisal

MITCHEL DRUCKER, M.D. AND ROBERT C. WALLACH, M.D.

Abstract

Intracavitary uterine packing was used for the control of hemorrhage in thirteen cases. In only two cases was the technique ineffective, and in these, occult cervical lacerations were found and repaired transabdominally. Morbidity was acceptable and no hysterectomies were performed. Despite generally unfavorable comments in the literature, uterine packing should be considered for control of uterine hemorrhage of obstetric cause for selected indications.

Introduction

The control of uterine hemorrhage by the use of an intracavitary pack has been used by obstetricians for over a century. This technique was quite popular during the early 1900's, but has since fallen into disfavor (1-6). The experience of this department over a one-year period was reviewed in order to evaluate the efficacy of uterine packing.

Materials and Methods

In a period of twelve months from June 1976 through June 1977, there were thirteen cases of uterine hemorrhage treated with intracavitary packing.

The uteri were packed either transvaginally following suction curettage, normal spontaneous vaginal delivery, dilatation and curettage, or, transabdominally at the time of cesarean section. Nonmedicated dry gauze was used as the packing material. There were two methods of transvaginal uterine packing employed in this series. The first required the use of a tubular packer such as the Holmes packer. The cervix was exposed and securely grasped with a tenaculum or sponge forceps. The stylet of the packer was used to gently introduce dry gauze packing into the uterus. The packer would then be gradually expelled from the uterus as the packing accumulated. The uterus was packed tightly.

The second method of transvaginal packing utilized a dressing or packing forceps. The dry gauze packing was ntroduced into the uterine fundus by the packing forceps. The gauze was advanced into the uterus with short strokes of the forceps. The tips of the forceps were not withdrawn from the uterus until it was tightly packed.

If packing was required at the time of cesarean section, the end of a roll of dry gauze packing was grasped with a dressing forcep and passed transcervically into the vagina. This forcep was then removed from the operative field and the uterus was manually packed: first the lower uterine segment and then the fundus.

Prophylactic antibiotics were started at the time of uterine packing in all cases. Intravenous oxytocin was continued for 12 to 24 hours after pack insertion.

The pack was removed at the patient's bedside or in the operating room. The patients received diazepam (dose: 10 mg intramuscular (IM) or intravenous (IV) and/or meperidine (dose: 75 mg IM) prior to the procedure. The pack was manually removed transvaginally, gently and slowly. Intravenous oxytocin was administered 12 to 24 hours after pack removal. Care was taken to insure that the gauze packing was completely removed.

Results

Table I summarizes the thirteen cases of uterine packing in this series. Hemorrhage due to uterine atony was diagnosed in nine cases, placenta previa with persistent bleeding from the placental site in two cases, and occult deep cervical lacerations in two cases. Ten patients were packed transvaginally and three were packed transabdominally at the time of cesarean section.

The two cases of pack failure were due to deep cervical laceration undiagnosed at the time of uterine packing. Both of these patients had exploratory laparotomy with repair of the defect and bilateral hypogastric ligation.

There were two cases in which a temperature of 103° Fahrenheit (F°) within 12 hours of pack insertion was recorded. In each case the temperature returned to normal within 24 hours. The highest temperature recorded in the remaining cases was 100.8 F°. None of the patients'

From the Department of Obstetrics and Gynecology, Beth Israel Medical Center, and Mount Sinai School of Medicine of The City University of New York, New York, N. Y. 10029.

Requests for reprints should be sent to: Robert C. Wallach, M.D., Department of Obstetrics and Gynecology, Beth Israel Medical Center, 0 Nathan D. Perlman Place, New York, N. Y. 10003.

TABLE IA

Thirteen Cases of Uterine Packing

Patient No.	Age	Parity	Procedure prepack	#Units blood	Transabdominal/ vaginal
1	35	4034	suction curettage	2	vaginal
2	25	2002	suction curettage	3	vaginal
3	27	1021	dilatation & curettage	1	vaginal
4	25	1111	hemorrhage post cesarean section	4	vaginal
5	24	1011	cesarean section for placenta previa	9	abdominal
6	27	1011	dilatation & curettage for incomplete abortion	2	vaginal
7	45	0010	cesarean section for placenta previa	2	abdominal
8	24	0030	dilatation & curettage for incomplete abortion	2	vaginal
9	44	0020	cesarean section for breech; myomata uteri	2	abdominal
10	23	1011	normal vaginal delivery	2	vaginal
11	28	1001	incomplete abortion	2	vaginal
12	33	2022	dilatation & curettage for incomplete abortion)	0	vaginal
13	28	0000	dilatation & curettage for incomplete abortion	3	vaginal

TABLE IB

Thirteen Cases of Uterine Packing

Patient No.	Vaginal Pack	Highest Temp	Highest WBC	No. hours packing in-situ	Antibiotics	No. days in hospital post pack insertion
1	Yes	100.6	9300	96	ampicillin	8
2	Yes	103.0	12300	96	tetracycline	8
3	Yes	98.6	7900	48	ampicillin	3
4	Yes	100.6	15600	24	ampicillin	7
5	No	103.0	19600	48	ampicillin	7
6	Yes	98.8	18600	96	ampicillin	8
7	No	100.0	22000	72	keflin	7
8	No	100.0	6800	24	keflin	1
9	Yes	100.6	20800	72	keflin	10
10*	-	-	-	-	-	-
11	Yes	100.8	12000	48	ampicillin	7
12	Yes	99.2	20000	24	ampicillin	2
13*	-	-	-	-	-	-

* Pack failure in 2 cases of cervical laceration (see text).

hospitalizations was prolonged due to fever. The packing was left within the uterus for 24 hours in three cases, 48 hours in three cases, 72 hours in two cases, and 96 hours in three cases. Factors determining the time interval included availability of supporting staff and physician decision.

Hemorrhage following pack removal did not occur although preparations for this were always made. All but three cases had a vaginal pack inserted in addition to the uterine pack. There were no cases of uterine perforation at the time of packing.

TABLE II

*Etiology of Uterine Atony**

I. anesthesia
II. prolonged labor
III. precipitate labor
IV. myomata uteri
V. overdistention of the uterus
VI. abruptio placenta
VII. congenital anomalies of the uterus
VIII. multiparity
IX. idiopathic

* Modified from Posner (7).

Discussion

In our recent experience, uterine packing was employed in cases of placenta previa with uncontrolled hemorrhage from the placental site and hemorrhage secondary to uterine atony. The causes of uterine atony ar listed in Table II. Prior to ascribing the hemorrhage t either of these two diagnoses, however, the operator mus eliminate all other causes of genital tract hemorrhage. Therefore, before packing, the physician should routinely perform the following diagnostic and treatment techniques:

1. Careful inspection of the vulva, vagina, and cervix for any sign of laceration or abrasion.
2. Exploration of the uterine cavity for retained products of conception, placental secundines, perforation, rupture, or inversion.
3. Parenteral administration of oxytocin and/or ergot alkaloids in order to stimulate uterine contraction.
4. Manual stimulation and compression of the uterus. The uterus should be held cephalad in order to keep the uterine arteries on "stretch." Theoretically, this diminishes the bore of the uterine arteries, thus decreasing the blood flow to the uterus. (The vaginal pack used in eight cases in this series is ntended to keep the uterus in a cephalad position).
5. Evaluation of the patient's clotting mechanism to be certain that no coagulopathy exists.
6. Monitoring of the patient's vital signs, central venous pressure (CVP), urine output, etc. and administration of fluids, electrolytes and blood as required.

This recent experience indicates that uterine packing can be effective in controlling hemorrhage due to uterine atony and bleeding from the placental site with an acceptable morbidity.

Most modern authors, however, believe that uterine packing is ineffective and leads to an increased morbidity. They maintain that uterine packing causes uterine distention rather than stimulating contraction; hides uterine bleeding; leads to infection; and, causes loss of valuable ime in the control of hemorrhage.

In this series there was no evidence of concealed hemorrhage behind the pack or an increase in uterine size after pack insertion. Furthermore, in all cases the uterus was packed tightly, and we believe that this is essential f uterine packing is to be successful. No excessively vigorous manipulations were performed, however, for an atonic uterus may be readily perforated.

In the two cases in which the pack failed to control hemorrhage, bleeding was visible externally within 30 minutes of pack insertion and exploratory laparotomy was promptly performed. These cases occurred despite careful inspection of the genital tract prior to uterine packing as the endocervix could not be seen. The morbidity due to febrile episodes was attributed to local nfection and was not of great consequence.

Certain authors have also maintained that uterine packing remains a valuable technique. Lester, Bartholomew, et al reported 135 cases of postpartum hemorrhage due to uterine atony and placenta previa treated suc-essful with uterine packing (9). They reported 28 addi-ional cases of packing for other indications. There were wo failures in this group. One was due to coagulopathy nd the other was complicated by amniotic fluid embo-ism. Hysterectomy was not required in any of these cases. Pierce and Winkler reported 505 cases of hemorrhage postpartum secondary to uterine atony in a series of 38,403 deliveries (10). The treatment for these patients was uterine packing and there were no hysterectomies performed in any of these patients.

In 1955, Benaron used oxidized cellulose to pack 50 uteri (11). It was successful in 48 cases. This packing material was noted to be particularly useful at the time of cesarean section, for the uterus could be rapidly closed without worry of catching the pack with a suture. The packing material was spontaneously expelled from the uterus with 72 hours.

Taylor reported in 1960, that in his experience with over 65,000 deliveries, there were no hysterectomies performed on normal uteri for postpartum hemorrhage due to uterine atony. He attributed this to be prompt and efficient use of uterine packing. Hester, in 1974, reviewed his experience with 32,799 deliveries over nine years (8). A total of 33 uteri were packed. Thirty were packed with a diagnosis of uterine atony, two had placenta accreta, and there was one uterine rupture. Hysterectomy was employed in the case of placenta accreta and uterine rupture. The remaining patients needed no further therapy to control bleeding. Endometritis did not occur in any of the patients packed.

Most of the previously cited authors recommend removal of the pack within 24 to 48 hours. Douglas and Stromme, however, remove the pack within a few hours of insertion (13). They believe its hemostatic effect is accomplished in this time.

The mechanism of action of the intrauterine pack is unclear. One proposal is that the pack, acting as a foreign body, stimulates the uterus to contract in order to extrude it. Another theory maintains that the pack tamponades the blood flow from the uterine vessels. This allows the blood to clot within the vessels, thus halting the hemorrhage.

In conclusion, when nonsurgical methods of active management have failed to control uterine hemorrhage due to atony, or bleeding from the placental site with placenta previa, uterine packing has been an effective technique with an acceptable morbidity. This technique may permit the physician to avoid a laparotomy and the possible complications involved with pelvic side wall dissection and hypogastric or uterine artery ligation. It also may permit the preservation of the uterus in those cases in which hysterectomy would be a tragedy.

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Combined Granular Cell Tumor of the Stomach and Cecum

ALI GHAZI, M.D., F.A.C.S.

Abstract

A 36-year-old female was hospitalized because of bright red rectal bleeding. A cecal lesion was demonstrated by barium enema as well as colonoscopy. Repeat endoscopy revealed a gastric lesion along with multiple cecal lesions. They proved to be granular cell myoblastoma. Surgical management of the case, and radiologic and endoscopic appearance of these tumors are discussed.

Granular cell myoblastoma, or more correctly, granular cell tumor of the gastrointestinal tract, is a rarity. There have been reported cases of granular cell tumor of the stomach and a few published reports of solitary granular cell tumor of the cecum (1, 2). However, a search of the iterature failed to show any published report of combined and multiple granular cell tumors of the stomach and cecum. To our knowledge, this is the first reported case.

Case Report

A 36-year-old white female was admitted to Beth Israel Medical Center on March 22, 1975, complaining of intermittent abdominal epigastric pain together with a history of two episodes of bright red bleeding from the rectum.

The patient's first episode of bleeding occurred in June 1974. There was no previous history of peptic ulcer disease. A barium enema examination of the colon demonstrated a small lesion of the cecum, most likely a polyp Fig. 1). On August 6, 1974, the patient was colonoscoped and a 1.5 cm in diameter, firm and mobile submucosal esion of the cecum was found which appeared to be a eiomyoma (Fig. 1A). A biopsy of the mucosa overlying he lesion revealed normal colonic mucosa. Reexaminaion in six months by colonoscopy was recommended.

The patient was reexamined on January 17, 1975, and colonoscopy revealed three smooth submucosal polypoid esions in the cecum, the largest of which now measured .7 × 1.5 cm (Fig. 2). This larger lesion showed a few mall ulcerations and evidence of recent hemorrhage. All three lesions had a hard consistency and all were whitish and smooth in appearance. The patient remained anemic with her hemoglobin ranging from 11.2 gm% to 12 gm%. Her abdominal pain persisted.

She was admitted to Beth Israel Medical Center for colon resection. As part of her work-up she underwent an esophagogastroduodenoscopy to rule out other sources of bleeding. Gastroscopy revealed a 1.5 × 2 cm raised, firm lesion in the upper body of the stomach that was located near the greater curvature on the posterior wall of the stomach. The lesion had a central ulcer. The gross appearance of the lesion was that of a leiomyoma with central ulceration. The patient also had a healing antral erosion. It was decided to treat her conservatively until the antral erosion had healed. She was discharged and followed as an outpatient. Subsequently, the patient did well and repeat gastroscopy showed that the antral erosion had completely healed.

She was readmitted on March 22, 1975, for elective surgery of both gastric and cecal lesions. On admission, her hemoglobin was 12.6 gm%, white blood cells were 10,700 cc with a normal differential count. Her systemic multiple analysis of 12 was within normal limits. Urinalysis, blood urea nitrogen, fasting blood sugar, and all other laboratory data were within normal limits.

The patient underwent surgery on March 24, 1975, when a local excision of the gastric lesion including a rim of normal gastric wall, and a resection of the cecum together with a portion of terminal ileum and ascending colon was performed. An end-to-end ileoascending colostomy and a tube gastrostomy was performed.

Pathologically, the resected gastric specimen measured 3.5 cm. The lesion was well circumscribed, greyish white in color and measured 2.5 × 2.5 cm. The gastric mucosa covering the lesion was congested and showed pinpoint hemorrhages. The cut surface showed a well circum-

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From the Department of Surgery, Beth Israel Medical Center, New York, N.Y. 10003.

Requests for reprints should be sent to Ali Ghazi, M.D., Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, N.Y. 10003.

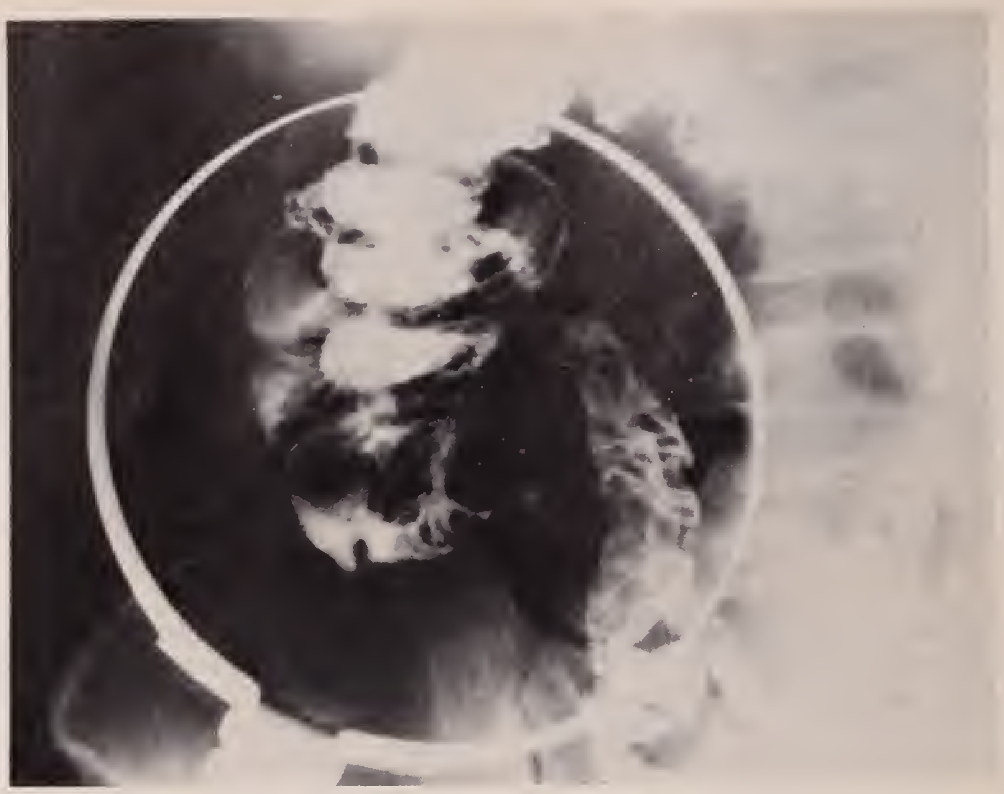

FIG. 1. Spot film of cecum revealing a round filling defect of the cap, interpreted as possible polyp by radiologist.

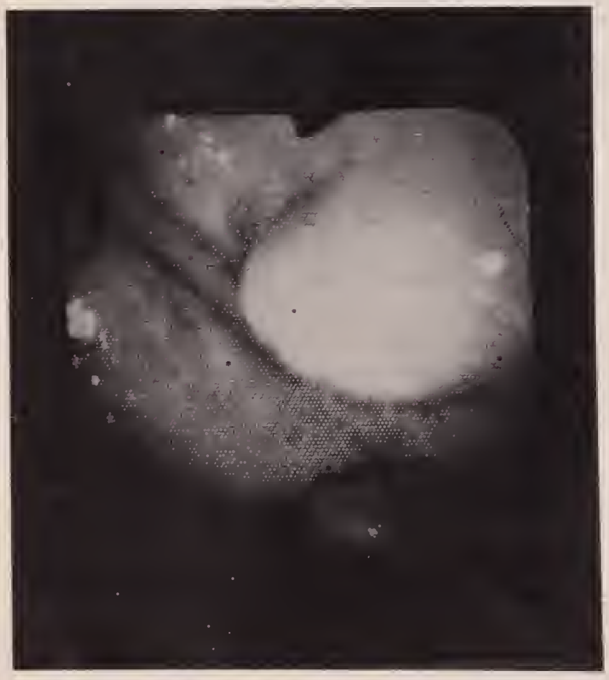

FIG. 1A. Endoscopic view of the cecal submucosal mass proved to be granular cell tumor by subsequent surgery. Note the submucosal location of the mass which is covered by pale whitish mucosa.

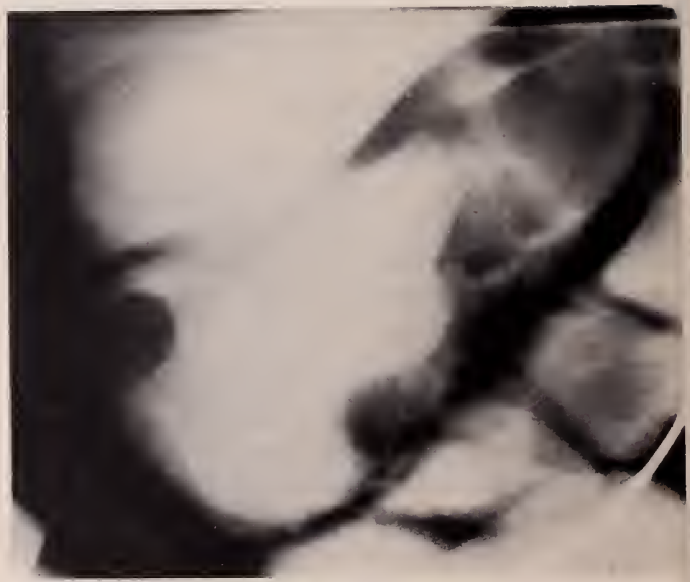

FIG. 2. Barium enema (close-up photograph of cecal cap) showing three round filling defects of the cecal cap.

scribed intramural white color mass (Fig. 3). Histology revealed it to be a granular cell myoblastoma of the stomach with evidence of healed ulceration.

The second specimen that included cecum, appendix and terminal ileum was described as follows: "The cecum measures 6 × 11 cm in dimension. The mucosal surface of the cecum shows well circumscribed whitish nodules that are raised above the surface with a diameter of 1.5 cm in diameter. The serosal surface shows dilated blood vessels but otherwise is grossly normal." Histology of these specimens also revealed "multiple granular cell myoblastoma of cecum (5X) with evidence of healed ulceration." Two of the five tumors measured 0.5 cm and, because of the small size, they were not diagnosed on endoscopy (Fig. 4).

The patient had an uneventful postoperative course. She was discharged on the fourteenth postoperative day without any complications. The patient had a follow-up endoscopy performed in December 1975, and it revealed no abnormal findings in the stomach or colon. The ileoascending colon anastomosis revealed no evidence of any abnormality.

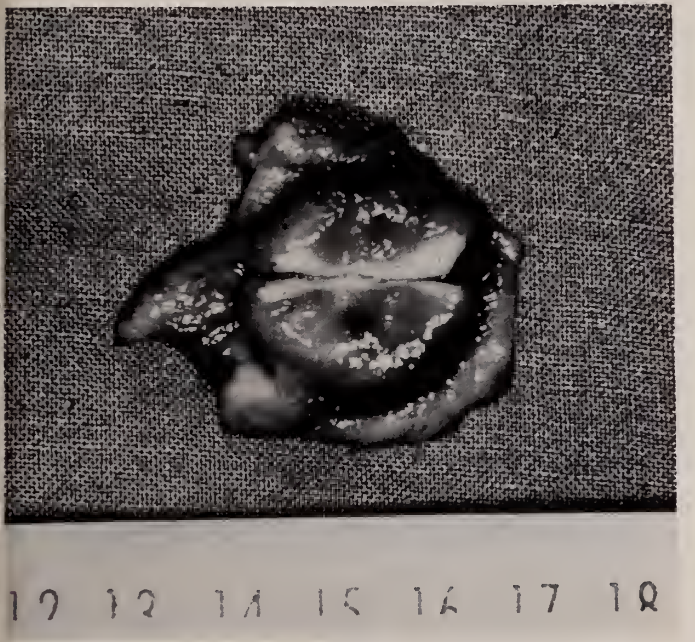

FIG. 3. Granular cell myoblastoma of stomach with evidence of central ulceration. The cut surface reveals whitish, hard intramural mass.

Discussion

Granular cell myoblastoma was first described by Abrikossoff in 1926 and again in 1931 (3, 4). The majority of the cases occur in the oral cavity, gastrointestinal tract, and breast. The bronchus, urinary bladder, vulva, gallbladder, cystic and common bile ducts, thyroid gland, parotid gland, and pituitary gland rarely may be the origin of this tumor.

Abrikossoff believed that these tumors arose from myoblasts which are the precursor cells of the adult striated muscle. Microscopically, they consist of polygonal cells with characteristic highly granular cytoplasm, hence the name granular cell myoblastoma. The hypothesis was unchallenged until 1962 when Fisher and Wechsler, using electron microscopy, found Schwann cells and axons in these tumors (5). There are many published reports now using either electron microscopy or chemical and histochemical methods to find similarities between granular cell myoblastoma and tumors of neural cell origin (2, 6, 7).

Many authors now believe that granular cell tumors have a neural rather than a myoblastic origin, but this difference of opinion has not yet been completely settled and it may be many years with much more extensive work before this can be finally settled (2). The World Health Organization (WHO) has classified this tumor as "tumor of unsettled origin", but there is no dispute that they are all neoplastic.

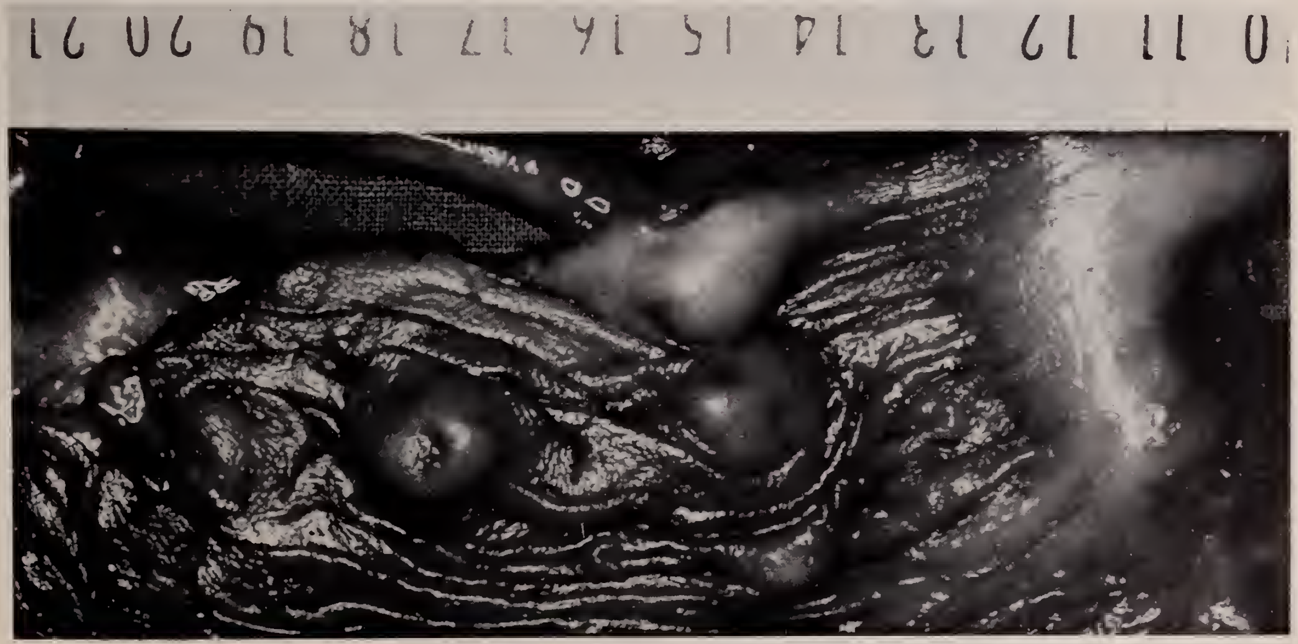

FIG. 4. Excised cecum, showing several submucosal granular cell tumors, the largest of which shows central dimpling and ulceration of mucosa with evidence of pinpoint hemorrhage.

When this tumor is located in the stomach, abdominal pain and anemia are part of the symptomatology, but gross gastrointestinal bleeding is rare. One may attribute the patient's acute gastrointestinal bleeding to these tumors, but this is far from proven, though evidence of ulceration of both gastric and colonic lesions were demonstrated endoscopically and pathologically. If there was no evidence of an antral erosion, one could have assumed that these lesions were the only source of bleeding. However, there was no active bleeding at the time of endoscopy from any of the gastric or cecal lesions. One may cautiously state that since bleeding was bright red and was not a major bleed, thus requiring transfusion, it could, therefore, have come from the lower gastrointestinal tract, possibly the cecal granular cell tumors. However, this is only conjecture.

Finally, one should be aware of the difficulty that the endoscopist may have in the differential diagnosis of these submucosal masses. Most submucosal masses are covered by normal appearing mucosa. In fact, mucosal biopsy does not reveal the true nature of these lesions and one should consider the diagnosis of granular cell tumors whenever he confronts a submucosal hard mass in any area of the gastrointestinal tract, especially the esophagus, stomach or colon (1, 2).

In treating these lesions, if they are incidental findings at radiology or endoscopy, one may safely follow these small tumors because malignant transformation in the gastrointestinal tract is extremely rare. On the other hand, if abdominal pain or anemia persists, one may proceed to local excision, including small portion of healthy tissue around the mass. Since malignant granular cell myoblastoma of the gastrointestinal tract has not been reported, extensive radical surgical excision should not be contemplated.

Summary

The first case of combined single gastric granular cell and multiple colonic granular cell tumors is reported. Endoscopic, as well as radiologic, appearances are demonstrated. The possible origin of these neoplastic tumors, ulceration and acute G.I. bleeding from these benign tumors are explained.

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Liposarcoma of the Spermatic Cord: Report of a Case and Pitfalls in Sonographic Differential Diagnosis

FRANKLIN TURETZ, M.D., JAN J. SMULEWICZ, M.D. AND HUBERT HECHT, M.D.

Introduction

Spermatic cord tumors are infrequent neoplasms, of which less than 200 cases have been reported in the literature. About 50% of all primary spermatic cord tumors are malignant and most representing sarcomas (1). Carcinomas, seminomas, teratomas, and various other tumors are very rare (2). Of the sarcomas, only three liposarcomas have been reported prior to 1971, and none since then (3). We had the opportunity to examine one case of spermatic cord tumor, histologically a liposarcoma. In addition to its rarity, this is to our knowledge, the first cast of spermatic cord tumor in which sonographic findings and sonographic differential diagnosis are presented.

Case Report

Patient A: A 58-year-old white male was admitted for removal of a painless right supratesticular mass. The mass had been discovered by the patient, who stated that it had doubled in size in four months.

Physical examination revealed a painless, firm supratesticular mass that did not transilluminate. There was no inguinal adenopathy. Laboratory studies and x-rays (I.V.P. and chest) were normal. Ultrasound at high gain revealed a sonolucent mass with excellent sound transmission (Fig. 1). Despite the somewhat irregular borders, this was interpreted most likely to be cystic.

Operative procedure consistent of a right orchiectomy and ligation of the cord. The tumor was 6 × 5 cm and the cut surface showed a greyish white appearance with areas of hemorrhage. The tumor was separate from the testicle, epipidymis and vas deferens (Fig. 2). Histologic diagnosis was malignant mesenchymal tumor of the spermatic cord, consistent with liposarcoma. Blood vessel invasion and lymph nodes metastases were found.

Of interest is the period of rapid growth that could be accounted for by the theory that most liposarcomas of the cord arise as benign lipomas that subsequently undergo malignant transformation (3). Also of interest is that blood vessel invasion and lymph node metastases were found. Banowsky, in discussing the advisability of retroperitoneal nodes dissection in spermatic cord tumors, reported this to occur in 29% of their studies (4).

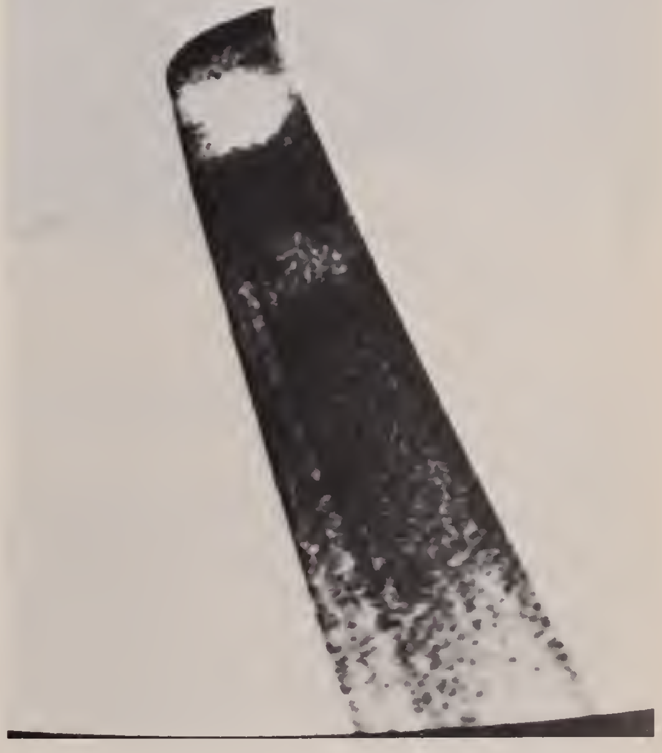

FIG. 1. Patient A: Transverse scan through the mass.

The cystic appearance on sonography is explainable by the homogeneous nature of the tumor. Sarcomas, in common with lymphomas, can have a cystic sonographic appearance. Any physically homogeneous tumor, espe-

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From the Department of Radiology and the Department of Urology, Beth Israel Medical Center, New York, N. Y. 10003.

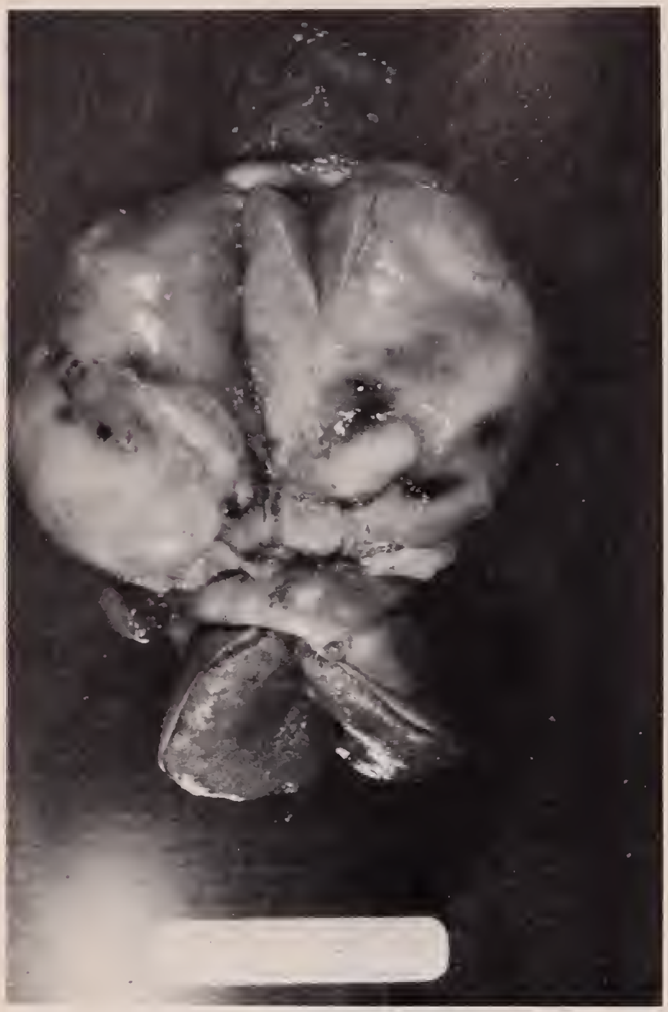

Fig. 2. The opened testicle is seen inferiorly. Just above the testicle, note the epididymis. The large mass above the epididymis represents the cut surface of the tumor.

cially lymphomas and sarcomas, can look cystic (5). The liposarcoma was similar in appearance to another supratesticular mass that was examined.

Patient B: A 35-year-old white male was admitted six months after right radical orchiectomy for seminoma of the testicle. The patient had a testicular prosthesis inserted at the time of the orchiectomy. Subsequently, the patient developed a painless 3 to 4 cm mass that transilluminated. The sonogram showed a 4.2 cm, well defined sonolucent area with smooth borders and excellent sound transmission. This was interpreted as cystic (Fig. 3). The mass was excised and the pathologic diagnosis was hematocele.

The sonographic error in Patient A could have been avoided had a 5 mHz transducer been used in addition to the 3.5 mHz transducer. Solid, though lucent masses, show increased attenuation at higher frequencies. A truly cystic mass will show no change in transmission. In addition, more attention should have been paid to the border of the lesion.

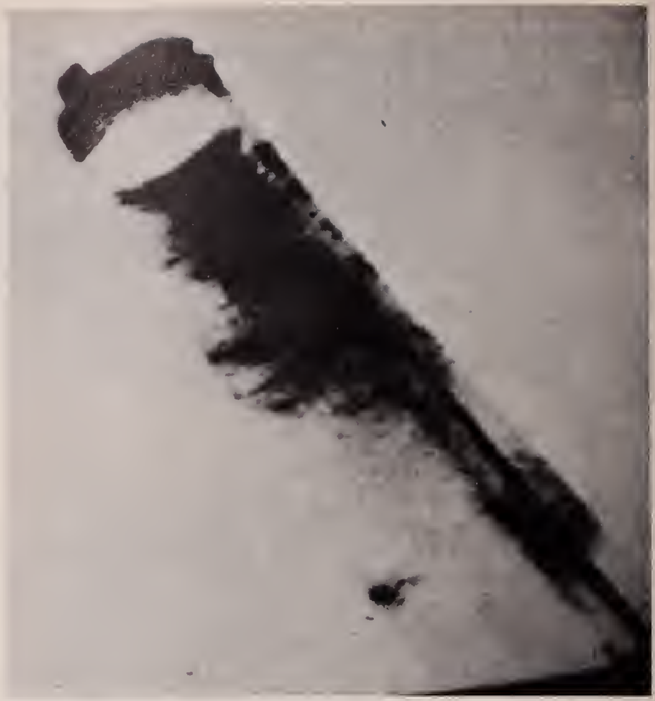

Fig. 3. Patient B: Transverse scan through the mass.

Summary

A case of liposarcoma of the spermatic cord has been presented and a pitfall in sonographic diagnosis has been illustrated.

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Acute Syphilitic Meningitis: A Case Report

ELLEN T. MELVIN, M.D., and DONNA MILDVAN, M.D.

Abstract

Because of its infrequent occurrence, we present an interesting case of acute syphilitic meningitis.

Introduction

Aseptic meningitis still presents a challenge to the clinician. The constellation of fever, meningeal signs and mononuclear cell pleocytosis of the cerebrospinal fluid is produced by a variety of infective agents and noninfectious processes. Viral infections (primarily coxsackie, echo, mumps, nonparalytic polio and lymphocytic choriomeningitis) together with leptospirosis, account for 95 percent of cases of aseptic meningitis that have an established etiology (1). The more uncommon etiologies can often be excluded on the basis of known exposures, seasonal variation of certain infections and the accompanying complex of symptoms and physical findings.

The clinical manifestations of syphilis, a disease reported to be increasing in many urban areas (2), may be so variable that this diagnosis is not often considered as a cause of aseptic meningitis. The following case is presented as an uncommon manifestation of this common disease.

Case Report

The patient is a 29-year-old white male who was admitted to Beth Israel Medical Center in July 1978 for the sudden onset of fever, severe frontal headache and photophobia of less than 24 hours' duration. Review of systems was negative for chills, rash, pharyngitis, and for genitourinary, gastrointestinal and upper respiratory complaints. There was no history of exposure to tuberculosis.

His past medical history was positive for gonorrhea twice, two and four years prior to admission, treated each time with penicillin injections. The patient reported having had a negative VDRL at the time of his last treatment for gonorrhea. He acknowledged recent sexual activity with many different partners. The patient had moved to New York City two months prior to admission, after having lived in Atlanta, Georgia for two years. A history of extensive foreign travel in the past was noted.

On admission, the patient had an oral temperature of 101.6° F. and complained of headache and neck stiffness. He was a healthy appearing white male with normal mental status. Examination of the fundi showed no evidence of papilledema. Minimal photophobia was present and meningeal signs were moderate. No other neurological deficits were noted. The skin and mucous membranes were free of lesions; the pharynx was clear. Bilateral shotty, nontender adenopathy was present in the cervical and inguinal regions. The remainder of the examination revealed no abnormalities.

Laboratory data showed a white blood cell count of 9,300 per cu mm with 2 percent stabs, 73 percent polymorphonuclear cells, 25 percent lymphocytes; the hematocrit was 41 percent; the sedimentation rate was 5 mm in one hour. Chest roentegenogram was normal. Lumbar puncture performed on admission revealed an opening pressure of 160 mm H_2O, glucose of 70 mgm percent, (serum glucose was 99 mgm percent), and protein of 56 mgm percent. The cell count showed a total of three red blood cells and 441 white blood cells per cu mm with 92 percent lymphocytes. Neither the India ink preparation nor the gram stain revealed any organisms.

The admitting diagnosis was aseptic meningitis, of possible viral etiology. Antibiotics were withheld and specimens were obtained for viral isolation. The neck stiffness and photophobia improved within 24 hours of admission, but the headache remained severe and the fever rose to 102° F. and persisted for the succeeding six

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From the Division of Infectious Diseases, Department of Medicine, Beth Israel Medical Center; and the Department of Medicine, Mount Sinai School of Medicine, of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to Dr. Donna Mildvan, Division of Infectious Diseases, Department of Medicine, Beth Israel Medical Center, New York, N. Y. 10003.

days. Cultures of blood, throat, urine, and cerebrospinal fluid were negative for bacteria. Sera for heterophile and HB_SAg were negative, as was the reaction to a 5 TU tuberculin skin test. Static and dynamic brain scan showed no abnormalities. On hospital day seven, a repeat lumbar puncture yielded the following data: glucose of 46 mgm percent, protein of 92 mgm percent, fresh red blood cells of 2,411 per cu mm, white blood cells of 575 per cu mm with 95 percent lymphocytes. The gram stain, acid fast smear, and India ink preparations were again negative. The serum VDRL drawn on admission was reported at this time as positive at a dilution of 1:32 with a positive FTA, and the diagnosis of syphilitic meningitis was now entertained. In this regard, cerebrospinal fluid from the second lumbar puncture showed a positive VDRL at a dilution of 1:2, and a positive FTA.

A ten-day course of intravenous aqueous penicillin was recommended but the patient refused continued hospitalization. Therefore, a course of 7.2 million units of benzathine penicillin was given: 2.4 million units by intramuscular injection at weekly intervals for three doses. Within 24 hours of his first penicillin injection, on hospital day ten, the patient's temperature fell to 99° F. for the first time, and his headache dramatically disappeared. He was discharged the following day, feeling completely well and the recommended penicillin course was completed over the next two weeks. Cultures of the cerebrospinal fluid specimens were subsequently reported as negative for acid fast bacteria, fungi and virus; no virus was isolated from the rectal or throat swabs collected during the acute phase of his illness.

Discussion

Central nervous system syphilis is said to have accounted for ten percent of all neurologic consultations before effective therapy was available (3). Experience at that time showed that over 50 percent of syphilis of the central nervous system occurred within three years after the primary infection (4). There is substantial clinical evidence to support the fact that spirochetes lodge in the central nervous system early in the course of secondary syphilis. Mild meningeal symptoms may accompany the other manifestations of secondary syphilis in as many as 60 to 80 percent of cases. Spinal fluid changes occur in 30 to 50 percent of patients with syphilis of more than six months' duration. Most of these patients are asymptomatic and the spinal fluid may revert to normal without treatment (3).

Acute meningitis as the initial manifestation of syphilis is rare. In 1935, Merritt reported in one of the largest series compiled from three general hospitals, only 80 such cases over a 15-year period (5). In those patients with known date of onset of their primary infection, more than 50 percent developed meningitis within the first year of infection, with 75 percent of cases occurring during the first two years. It is interesting to note that acute meningitis was associated in this series with the rash of secondary syphilis in only six of 80 cases. The overall incidence of acute clinical meningitis in all patients with secondary syphilis is estimated to be only about one to two percent (1). The literature supports the fact that it is often difficult to assign a stage of disease to the patients who have neurologic involvement and unknown duration of infection. These patients are generally categorized as having neurosyphilis and treated with the maximum recommended benzathine penicillin doses intramuscularly or hospitalized for intravenous penicillin administration (6).

Representative cerebrospinal fluid findings can be taken from Merritt's series. The opening pressure was greater than 200 mm H_2O in two-thirds of patients. White blood cell count was between 100 to 1,000 in 65 percent of cases with ten percent having counts greater than 1,000. The majority of these cells were lymphocytes and monocytes. The protein was generally increased and ranged from 45 to 200 mgm percent. The cerebrospinal fluid glucose was often low with 55 percent of cases having values under 50 mgm percent. Other series report visualization of spirochetes in the cerebrospinal fluid of some patients (6).

Although activity of central nervous system infection in syphilis parallels cerebrospinal fluid pleocytosis and protein elevation, serologies are helpful in establishing syphilis as the cause of the neurologic problem.

The Wasserman and VDRL methods are the nontreponemal serologies most commonly used in testing the cerebrospinal fluid. These approach 100 percent specificity and 100 percent sensitivity in acute meningovascular and parenchymal neurosyphilis. These tests, however, are much less reliable in patients with late neurological disease when they may be negative in up to 20 percent of cases. The fluorescent treponemal antibody test (FTA), which is more sensitive than the VDRL in serum sample screening, has recently been applied to cerebrospinal fluid testing. The cerebrospinal fluid FTA is rarely reactive in nonsyphilitics, with a false positive rate of only 0.56 percent in a recent study (8). Cerebrospinal fluid serologies, therefore, are more helpful in diagnosing neurosyphilis than are serum serologies that may be suppressed by previous or suboptimal therapy and negative in late disease.

As in Merritt's series, in which 26 percent of patients with acute syphilitic meningitis had no historical evidence of prior syphilis, our patient gave a history of a negative VDRL two years previously and no history of a chancre or rash of secondary syphilis. On admission, he had none of the other signs or symptoms that are usually associated with secondary syphilis. The presence of fever does not necessarily suggest secondary disease since fever often accompanies early neurosyphilis when the disease is clinically active (4).

The cerebrospinal fluid results in our patient are consistent with those of syphilitic disease as described above. Since our patient had a traumatic lumbar puncture the question could be raised whether the positive cerebrospinal fluid serologies reflect contamination of the fluid with seroreactive blood. In a recent study, this question was investigated by the addition of small amounts of reactive blood to seronegative cerebrospinal fluid specimens up to a red blood cell count of 5,500 per cu mm (8). This resulted in no conversions of the cerebrospinal fluid VDRL. The FTA, however, could be converted to positive in the cerebrospinal fluid by the addition of blood. In our patient, therefore, the positive cerebrospinal fluid VDRL was considered diagnostic, and not the result of the traumatic lumbar puncture. His rapid clinical response to penicillin supports this interpretation.

Although the case we present demonstrates the classic features of syphilitic meningitis, this diagnosis was considered for the first time only when the routine serum serology was reported as positive. The patient was admitted in the summer when enteroviral infections are common, and the diagnosis of viral meningitis was so strongly favored that the initial cerebrospinal fluid specimen was not sent for serology. Although a recent editorial questions the practice of routine cerebrospinal fluid VDRL on all patients undergoing lumbar puncture, the present case underscores the usefulness of such testing in patients with neurological diseases of unclear etiology (9).

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Phycomycosis: A Case Report Combining Surgical, Therapeutic and Dental Management

MARY V. LAPINSKI, D.D.S.

Abstract

Rhinoorbital, cerebral phycomycosis is a relatively rare fungal infection seen in debilitated patients. Combined surgical and pharmacologic therapy is used since the course of the disease is rapid. A case report showing prosthetic replacements is presented.

Rhinoorbital, cerebral phycomycosis (mucormycosis) is a type of fungal infection that involves nasal, orbital, cranial, and oral structures. Mucor and rhizopus are of the phycomycetes class, have nonseptate mycelia, and are most often the causative genera (1). The disease progresses similarly from both organisms. Since fungi other than mucor are causative agents, the term phycomycosis was suggested as the preferred term but mucormycosis is still commonly used (2). These organisms are normally saprophytic and are seen on routine nasal, throat, and stool cultures. Under altered conditions they become opportunistic as in patients with diabetes, lymphoma, leukemia, sepsis, tuberculosis, and severe burns. However, diabetes remains as the most common underlying systemic disease. With regard to diabetes, there is some dispute as to whether the acidosis, the hyperglycemia or an unknown factor gives the predisposition to phycomycosis (3). In one study, all cases of phycomycosis occurred in patients with leukemia or lymphoma and only 54% of the patients had diabetes (4). Many are receiving antibiotics, corticosteroids, cytotoxic agents, and are severely debilitated (5).

Diagnosis of phycomycetes should be made upon evidence of positive culture and the microscopic picture. Therapy may be initiated upon clinical signs only, since the progression of the fungus is extremely rapid. Early diagnosis is essential for successful treatment. Current therapy for rhinoorbital phycomycosis includes surgical exenteration of affected tissues, intravenous therapy with amphotericin B, and control of underlying systemic disease if present.

Clinical signs and symptoms are varied and the following have been reported: crusting of the palate with black discoloration, swollen black turbinates or pale, whitish turbinates in the early, ischemic stages of the disease, ptosis of the lip and proptosis of the globe, loss of mobility of the globe, fixed and dilated pupils, nasal discharge with bloody elements, periorbital and perinasal swelling, cloudiness of the involved sinuses on radiographic examination without obvious fluid level and increasing lethargy. Most often the disease is seen unilaterally (Fig. 1) (6, 7).

Case Report

A 34-year-old black female came to the hospital with diabetes out of control and a swollen right eye with decreased vision of sudden onset. The patient was admitted to the hospital where the diabetes was controlled and ampicillin was prescribed for an eye infection. The patient was discharged in five days. The pain and swelling in her right eye continued and the decreased vision progressed to blindness. The patient then sought treatment by a private physician who referred her for admission. Initial examination revealed a large palatal erosion on the right maxilla, ptosis and proptosis of the right eye, right facial paralysis and anesthesia of the superior portion of the right face. Laboratory tests showed blood sugars of 400–500 mg%. Radiologic examination revealed soft tissue swelling in the right orbit, soft tissue haziness in the antrum, and bony erosion of the palate.

Phycomycosis was suspected from clinical evidence and although the initial biopsy of the palatal lesion did

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From the Department of Dentistry, Beth Israel Medical Center, New York, N.Y. 10003.

Requests for reprints should be sent to Mary V. Lapinski, D.D.S., Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, N.Y. 10003.

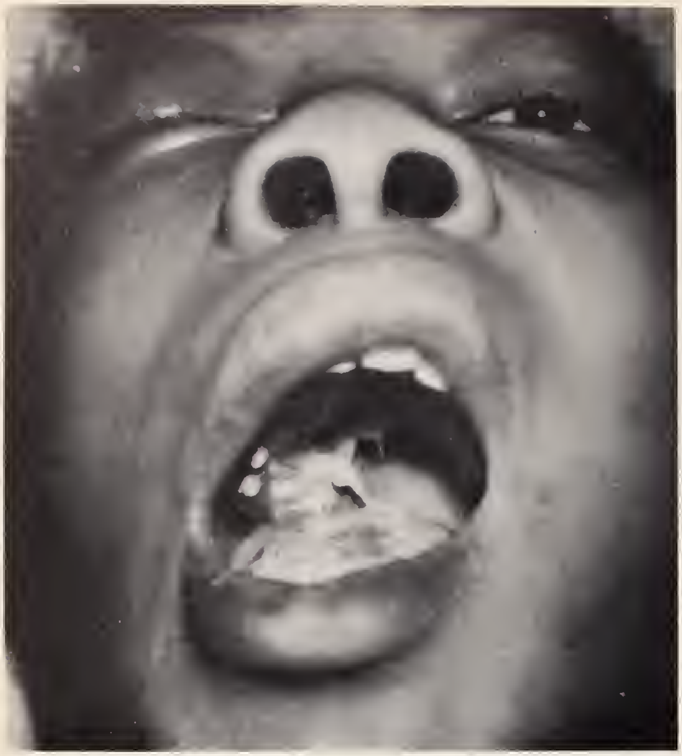

FIG. 1. The patient immediately preoperatively showing necrotic areas of the palate and proptosis of the right globe.

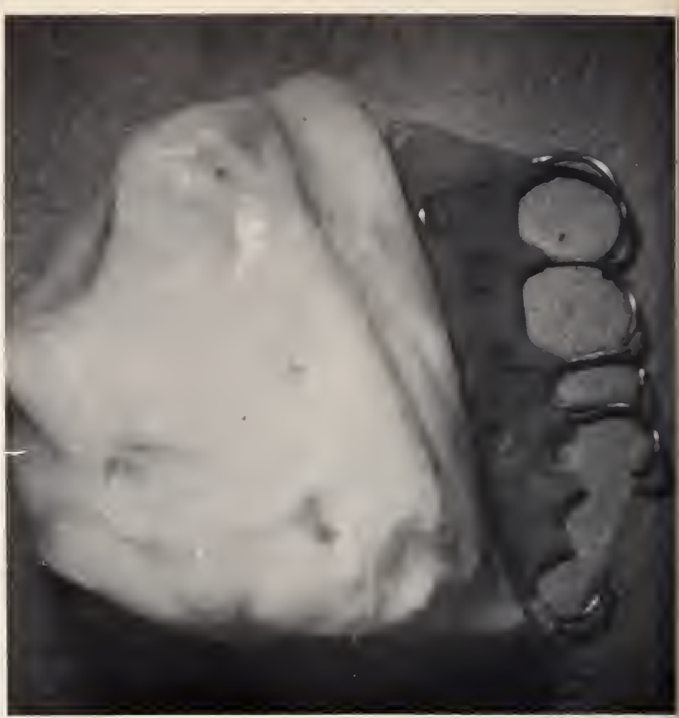

FIG. 2. The immediate surgical obturator with soft acrylic reline material.

not show phycomycosis, the patient was given intravenous doses of amphotericin B and was brought to the operating room where a right maxillectomy and orbital exenteration were performed. On microscopic examination of the specimen, nonseptate branching hyphae were identified but no growth was obtained in the laboratory.

Following surgery, the diabetes remained out of control. Other medical complications included intermittent nocturnal fever, hypokalemia and anemia that are often seen with amphotericin B therapy.

The patient was given a maxillary obturator at the time of surgery. Frequent adjustments were made immediately after the surgery because of the changing oral tissue. The appliance had wrought-wire clasps on the nonaffected teeth and an all acrylic base. The obturator was relined with a soft acrylic reline material and this was changed as required (Fig. 2). After several months, the patient was discharged in good condition and was able to function wearing the obturator and a patch over the right eye. Several months later, a new obturator was constructed with cast clasps, a hollow acrylic bulb, and teeth to replace those removed at the time of surgery. Due to the extensive nature of the orbital exenteration, it became necessary to construct an externally worn orbital prosthesis to replace the eye and the surrounding tissues. This appliance is kept in place with a surgical adhesive (Fig. 3).

Two and one-half years later, the patient shows no

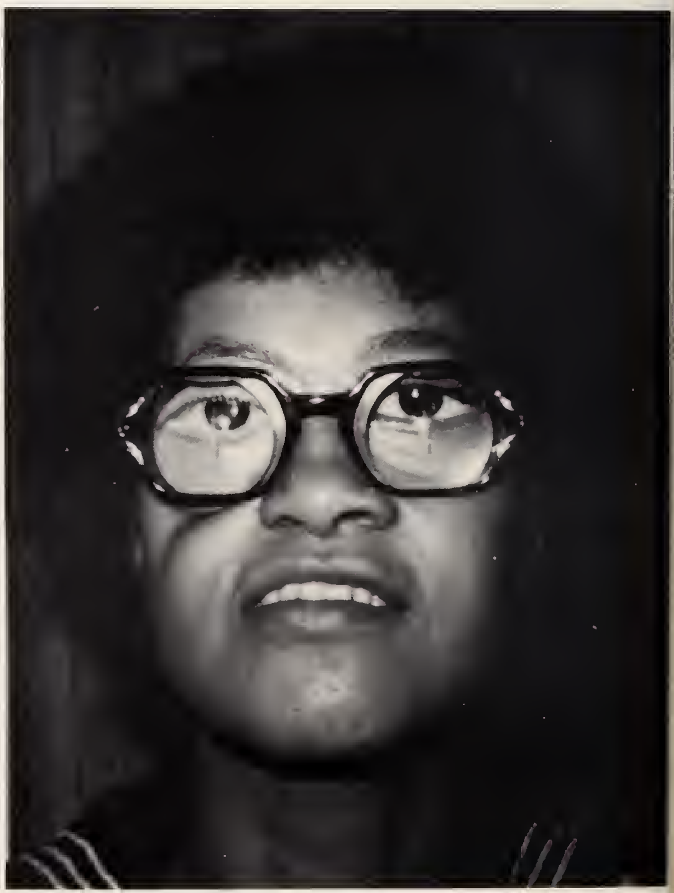

FIG. 3. Intraoral obturator and extraocular prostheses in place wit eyeglasses aiding in esthetics and function.

evidence of recurrent phycomycosis. The combined therapy of surgical exenteration, adequate dosages of amphotericin B, and control of diabetes has arrested this fungal infection.

Discussion

The most recent figures for survival of ROCP are around 50%. Early papers, prior to combined therapy, showed 80%–90% mortality (8). Today, there are increasing numbers of patients with a higher susceptibility for the disease. The early diagnosis and subsequent appropriate therapy can alter the morbidity and mortality. For patients who have required disfiguring surgical procedures, it is essential to provide adequate prosthetic replacements.

The immediate temporary or surgical obturator is constructed prior to the resection and is inserted while the patient is on the operating table. Thus, the wound is kept free of debris and food and surgical packs are kept in place. Soft tissue contours are maintained and nasal discharge is kept from flowing intraorally (9). Prompt resumption of normal oral function while speaking and eating allows for an easier transition and acceptance of an altered oral environment. Through careful construction of replacements, as well as psychological supportive therapy, patients will be able to function and accept the presence of the defect and prosthesis (10). It is only then that one can resume normal social activity.

Summary

Although still a rare disease, phycomycosis is diagnosed more frequently. Early recognition, treatment, and replacement therapy are essential for long-term patient care.

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HOSPITAL FOR JOINT DISEASE AND MEDICAL CENTER

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The Hospital for Joint Diseases and Medical Center

INTRODUCTION

Situated on the upper East Side of Manhattan, the Hospital for Joint Diseases and Medical Center occupies a unique position among the many medical institutions of New York City. Originally constructed in 1906 to specialize in orthopedic problems affecting New York residents, it developed rapidly into a treatment center for skeletomuscular diseases. Under the guidance of Joseph Milgram, the hospital's first full-time director, pioneering work was done on the total hip replacement operation in the United States. Notables in orthopedics joined the staff and helped in building its world renown–surgeon Leo Mayer, bone pathologist Henry Jaffe, and hand surgeon Emanuel Kaplan. The hospital's alumni have become leaders in orthopaedic surgery in major institutions and medical schools throughout the United States and foreign countries.

As the medical needs of the community grew more urgent, the hospital expanded its bed capacity to 330 beds and enlarged its outpatient services to provide for the general medical needs of the 200,000 residents of the East and Central Harlem area. Hospital for Joint Diseases further developed its community program with the establishment of a First-Chance Child Development Center, an Alcoholism Treatment Center, and a Drug Detoxification Department. Free services have also been provided for glaucoma and blood pressure tests.

Further broadening its perspective, a Research Institute was established in 1963, under the directorship of Dr. Vincent Hollander. Staffed by a dedicated group of scientists and after much hard work, the Institute secured a Core Grant for Cancer Studies from the National Cancer Institute to continue their many faceted investigations.

In November of 1964 the School of Professional Nursing was opened, creating a landmark in nursing education. It was the first school of its kind to permit Licensed Practical Nurses to become Registered Professional Nurses upon completion of a 12-month accelerated course approved by the New York State Department of Education. This came as an outgrowth of the Helene Fuld School of Practical Nursing which had begun operation in 1945. A school for the training of radiology technicians established in 1966, has also provided an excellent resource for the hospital's outstanding radiology department.

In 1967 the Hospital for Joint Diseases affiliated with Mount Sinai School of Medicine. A program of rotating residents was initiated and academic titles were given to senior staff, who have been actively participating in teaching, lecturing, and presenting seminars. The particular expertise of HJD's staff has undoubtedly been of great value to the medical school.

Vincent P. Hollander, M.D.

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Epidemiology, Management and Results of 200 Cases of Chest Trauma

NAVEEN DHAR, M.D., ALLEN ASHER, BA.,* DANIEL KRELLENSTEIN, M.D., Ph.D. AND
JOSEPH R. WILDER, M.D.

Abstract

This is a retrospective epidemiologic study of 200 cases of chest trauma seen during a six-year period at a community hospital in Harlem. Seventy-one percent of our patients were heroin addicts, alcoholics or both. Seventy-eight patients required some type of surgical intervention and thirty-nine underwent formal operative procedures. A consistently low mortality rate of only 2% in this high risk patient population has been attributed to very tight patient monitoring along with selective surgical intervention. Included in this study are nine patients who sustained injuries to the heart with no mortality.

Introduction

This is a review of 200 consecutive cases of chest trauma seen in the Department of Surgery of the Hospital for Joint Diseases and Medical Center (HJD&MC) in New York City from 1971 through 1976. The hospital is located in Harlem, an urban ghetto renowned for its violence and drug abuse. Of the chest injuries seen in civilian practice, the majority occur in automobile accidents (1). Our study, however, deals mainly with street violence, and thus, consists of a different type of wounds, such as stab wounds and gunshot wounds. This is because there is no ambulance service and we are situated far from any major highways. Patients who were dead on arrival were not included in this study. Patients seen in the emergency room and released because their injuries were minor were also not included.

Materials and Methods

One hundred and thirty-seven patients (63.5%) in this study were in the 21 to 40 year-old group (Table I). The average age was 33.7 years. Of the 200 patients, 171 (85.5%) were males and 29 (14.5%) were females. These figures are comparable to similar studies reported in the literature (2–4). One hundred and fifty-two (76%) of the patients in the study were Black, 45 (22.5%) were Hispanic and only 3 (1.5%) were Caucasian. The hospital receives patients mainly from the Harlem area, hence the racial distribution in this review reflects the general Harlem population (Table I). An analysis of the time of arrival of patients at the hospital revealed that 171 patients (85.5%) came between 6 p.m. and 6 a.m. This reflects the higher crime rate in the evening and early morning hours. A breakdown of the types of injury revealed 160 stab wounds (80%), 33 gunshot wounds (16.5%), one combination of stab and gunshot wounds (0.5%) and six cases (3%) of injuries due to falls or blunt instruments. Table I also shows that 71% of the patients in our series were addicted to alcohol and/or heroin, with alcohol addicts (32.5%) and dual addicts (both heroin and alcohol (31%)) making up the two largest groups.

Thirty-three patients (16.5%) had previous or later admissions to HJD & MC for violent trauma: twenty-five (12.5%) had at least one other admission before, during or after the period of study, and eight (4%) had more than one admission.

Description of the Injuries

Consistent with most studies on penetrating wounds of the chest, we saw a higher incidence of wounds of the left side of the chest (61%) than of the right (34.5%). Eleven patients (5.5%) had bilateral injuries. Cameron et al reported 72% left chest injuries, Gray et al, 61%, and Oparah and Mandal, 57% (4–6).

Multiple wounds of entry were sustained by 78 patients (39%). Nineteen of those patients had multiple injuries to the chest alone. Seventy-five patients (37.5%) had associated injuries to extrathoracic organs or structures. Of the 75 patients with extrathoracic injuries, 58 were from multiple wounds, and 17 from single wounds. Abdominal injuries were seen in 33 (16.5%) patients in our

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From the Department of Surgery, Hospital for Joint Diseases and Medical Center, and Mount Sinai School of Medicine, New York, N.Y.
* Mr. Asher is a third-year medical student.

TABLE I
Patient Data Base

Age Distribution		Race Distribution	
age in years	patients	Black	152
10–20	26	Hispanic	45
21–30	69	Caucasian	3
31–40	58		
41–50	25	Heroin and Alcohol Addiction	
51–60	16	Nonaddicts	58
61–70	5	Addicts	142
71–80	1	alcohol only	65
	200	dual (alcohol & heroin)	62
		heroin only	15
Average age: 33.7			200

series; Cameron et al reported 15.1% and Miller et al, 17.4%. These injuries, as will be shown, have a direct relationship to mortality figures (3, 5).

Thirty-three (16.5%) patients had significant hemorrhage and twenty-six patients (13%) came to the emergency room in shock. Other signs and symptoms included dyspnea, subcutaneous emphysema, hemoptysis and sucking chest wounds (Table II). The radiographic findings on admission are indicated at the bottom of Table II. Sixty-two of our patients (31%) showed pneumo-, hemo-, or hemopneumothoraces. Fourteen other patients developed hemo- and/or pneumothoraces, that were seen on subsequent chest radiographs. Other radiographic findings included subcutaneous emphysema, fractured ribs and foreign bodies.

Patient Management

Basic principles in the management of penetrating wounds of the chest as set forth by Sanger in 1944, have essentially undergone very little change (7). The philosophy of expectant observation, that is, treating patients nonoperatively and operating only for specific indications, has stood the test of time. This philosophy is in marked contradiction to that recommended by Schrire, who advocated operative intervention in all, or nearly all, penetrating chest injuries (8).

Indications for thoracotomy in our institution are:

1) Massive or continued hemorrhage
2) Injury to the heart
3) Injury to the esophagus
4) Injury to a major airway

Patients with chest trauma are evaluated and given basic resuscitation by the surgical team in the emergency room. After initial evaluation the patients are divided into two categories:

1) Patients not requiring immediate surgical intervention: these are put under strict observation; they are monitored in the intensive care unit, and have hematocrits and chest x-rays done at 4, 12 and 48 hours. This class of patients merits special mention because any significant lapse in observation of these patients can easily end in tragedy. Robicsek et al have reported a 12% mortality rate in patients managed expectantly (9). We had no deaths among patients in this category.

2) The second group is comprised of patients needing emergency surgical intervention (tube thoracostomy and/or exploration). All thoracotomy patients had thoracostomy tubes inserted in the emergency room prior to going to the operating room.

Of the 200 patients, 78 (39%) required some type of surgical intervention: 39 were treated with tube thoracostomy and 39 (19.5%) underwent major operative procedures (Table III). Patients suffering gunshot wounds required surgery more often than those who were stabbed (51.5 vs. 32.5%). Thirteen patients (6.5%) underwent thoracotomy with no operative mortality. The findings at surgery in our series of thoracotomy patients are listed in Table IV. All patients with clinical signs of cardiac injury were explored. Pericardiocentesis was used only as a temporizing measure to relieve pericardial tamponade while the patient was prepared for surgery.

Laparotomy was performed on 22 patients because of concomitant abdominal injuries. These patients merit

TABLE II
Admission Findings

Signs and Symptoms	Patients
significant hemorrhage	33
shock	26
dyspnea	17
subcutaneous emphysema	14
hemoptysis	4
sucking wound	2
Radiographic Findings	
Hemothorax	25
Hemopneumothorax	23
subcutaneous emphysema	13
pneumothorax	12
fractured ribs	11
foreign bodies (bullets)	8
hemothorax & pneumothorax*	2

* Not in the same hemithorax

TABLE III
Surgical Procedures

Treatment	Patients	
Tube thoracostomy	39	
Total operations	39	
Thoracotomy		13
Laparotomy & tube thoracostomy		9
Thoracotomy & laparotomy		8
Laparotomy		5
Exploration of neck (One with tube thoracostomy)		2
Exploration of axilla		1
Repair of hand injury		1
Total number of patients operated upon	78	

special mention since all four deaths in our series were in this group. This resulted in an operative mortality of 18% and an overall mortality of 2%.

Whenever both laparotomy and thoracotomy were necessary, we preferred making two separate incisions. A thoracoabdominal incision may predispose to pulmonary complications, and is not well tolerated by severely injured patients. Separate thoracotomy and laparotomy incisions not only give better exposure but also prevent thoracic contamination from possible perforated abdominal viscera. Only one of our eight thoracotomy and laparotomy patients had a thoracoabdominal incision. In this case the laparotomy incision was extended to the thorax in order to perform open cardiac massage.

The most frequently injured structure seen at laparotomy was the diaphragm, followed by the liver and the spleen. Table V shows the incidence of injury to the different abdominal structures caused both by thoracoabdominal wounds and by direct penetration of the abdomen (in the case of multiple wounds). Table VI indicates the organs injured with single thoracoabdominal wounds. Right-sided injuries totalled ten structures and included only the diaphragm and liver. Left-sided injuries totalled 30 structures and included injury to a wide variety of organs.

TABLE IV

Findings at Thoracotomy

	No. of Patients
myocardial injury	9
lung laceration	6
bleeding from coronary artery	2
bleed from internal mammary vessels	2
bleeding from scapular vessels	2
bullet in parietal pleura	1
bullet in mediastinum	1
CVP catheter in superior vena cava	1
bleeding from spleen through diaphragm	1

TABLE V

Findings at Laparotomy

Organs Injured	No. of Patients
diaphragm	16
liver	13
spleen	8
great vessels	4
stomach	3
kidney	3
splenic flexure of colon	2
pancreas	2

TABLE VI

Organs Injured with Single Thoracoabdominal Wounds

	No. of Organs Injured	
	Right	Left
diaphragm	5	11
spleen		6
liver	5	4
stomach		3
colon		2
kidney		2
pancreas		1
IVC & Portal Vein*		1

* Gunshot wound

Thirty-eight patients (19%) required blood transfusions: 23 patients (11.5%) received one to three units, and 15 patients (7.5%) received four or more units. The average hospital stay was 9.2 days.

Complications

The incidence of complications in our series was 7.5% (Table VII). The most frequent complications were wound infections (four patients) and recurrent hemothoraces (four patients). All the wound infections were at the site of injury. There were no infections in either the thoracotomy or laparotomy incisions. Four patients required thoracenteses after removal of the chest tubes for reaccumulation of fluid. Two of the three patients with pneumonia died. The patient with postpericardiotomy syndrome responded to steroids. Thoracotomy was successfully done to remove the tip of a CVP catheter broken by a patient.

Analysis of Mortalities

There were four deaths in 200 patients. An analysis of our mortality figures reveals all four patients had thoracoabdominal injuries. All of these patients were brought to the emergency room in shock and had extensive abdominal injuries involving multiple viscera in addition to their thoracic injuries.

Two of our patients expired during attempts at preventing exsanguination. One suffered a laceration of the liver and had a completely severed left kidney, and the other, a GSW patient, had a lacerated liver, portal vein, spleen and pancreas along with a hemothorax.

The other two patients died postoperatively because of pneumonia. The first of these had stab wounds of the chest and abdomen with hemothorax, a laceration of the diaphragm and of the right lobe of the liver. He underwent an exploratory laparotomy and a tube thoracos-

TABLE VII

Complications

wound infection	4
recurrent hemothorax	4
pneumonia	3
delayed hemorrhage from renal vessels	1
subphrenic abscess	1
postpericardiotomy syndrome	1
broken CVP catheter	1
	15 (7.5%)

tomy. On the second postoperative day he suddenly collapsed and expired. The autopsy performed by the medical examiner only revealed evidence of hypostatic pneumonia. The other patient died of extensive bronchopneumonia on the fourteenth postoperative day. His injuries included a left hemothorax and laceration of the diaphragm and of the left kidney.

Discussion

A retrospective study of all chest traumas encountered from 1971 to 1976 at the Hospital for Joint Diseases and Medical Center was carried out to examine the background of these injuries, their management and our results. Certain findings stand out: 1) There was a very high incidence of drug abuse in our patients; 2) There was no increase in the percentage of gunshot wounds during the period studied; 3) Left-sided injuries were more seriously damaging; 4) Thirty-nine percent of the patients required surgical intervention, half of these required major surgical procedures; and 5) The most commonly injured organ was the diaphragm.

Alcohol and Heroin Addiction

The percentage of heroin and alcohol addicts in our study, 71%, is extremely large. Miller at Harlem Hospital reported 29.7% heroin addicts (3). Seven and one half percent (7.5%) of our patients were heroin addicts and an additional 31% were dual addicts, giving a total of 38.5% for heroin addiction. One patient had had ten previous admissions at HJD & MC for alcohol, heroin, barbiturate and methadone addictions. (He died of multiple stab wounds on his eleventh admission.) When we compare the 71% addiction rate in patients with traumatic chest wounds to the 40% addiction rate of all patients on the surgery service at the Hospital for Joint Diseases and Medical Center, we see the positive correlation between drug abuse and chest trauma. (This is based on an analysis of 408 of the surgical admissions to the Hospital for Joint Diseases and Medical Center in 1976.)

Injuries

The 80% incidence of stab wounds is relatively high compared with 69% at Harlem Hospital (N.Y.C., 1973) and 56% at Martin Luther King, Jr. General Hospital (L.A., 1972–1975) (3, 4). These studies show an increase in the proportion of gunshot wounds in the last few years. Our statistics show no such trend throughout the six years of the study. Our higher incidence of stab wounds is consistent with statistics from older studies: 75% and 86% for Gray (1960) and Sherman (1966), respectively (6, 10).

Left- vs. Right-Sided Injuries

Wounds of the left side have been shown to be more serious than those of the right. Besides the fact that this is because of the location of the heart (seven of the nine cardiac injuries were due to left-sided wounds), the extent of thoracoabdominal injuries is different from one side to the other. On the right side the other contents of the abdomen are protected by the liver, which is usually the only intraabdominal organ injured in a right thoracoabdominal wound (Table VII). The contents of the left side of the abdomen are unprotected and injury to the different viscera is much more frequent. Sixteen of our patients (8%) had diaphragmatic injuries. These wounds may easily be missed and should be repaired to prevent late diaphragmatic hernias.

Cardiac Injuries

We agree with Oparah and Mandal that pericardiocenthesis is rarely useful for definitive therapy (4). Even as a diagnostic measure it can be misleading, especially if the blood in the pericardium is clotted. All suspected cardiac injuries in our series were explored. McNamara et al in their review of Vietnam War combat injuries considered cardiac tamponade as an indication for exploration; they reported only one death in thirteen patients (7.7%) with cardiac injuries (11). In our series, we treated two gunshot and seven stab wounds to various parts of the heart and all of the patients survived. Our 0% mortality is quite low compared to the values reported in other series. The average mortality calculated from fourteen different series reported in the literature from 1961 to 1977 is 25.9%, with a range from 7.7 to 40%.

Our overall mortality rate of 2% compares well with other reports on patients with similar injuries (Table VIII). Three reports average 5.4% mortality with a range from 1.5 to 16%. All deaths occurred in patients who had associated intraabdominal injuries.

TABLE VIII

*Mortality for Penetrating Chest Trauma**

Series and Year	No. of Patients	Mortality %
Cameron (1950)[5]	119	5
Farringer (1953)[12]	251	10
Gray (1960)[6]	769	3.8
Conn (1963)[2]	385	3.1
Beall (1966)[13]	921	6
Oparah (1976)[4]	200	1.5
Miller (1976)[3]	125	4
Kish (1976)[14]	380	2.5
Siemens (1977)[15]	190	16
Dhar (1978)	194	2.1
	Total: 3534	Average: 5.4

* Penetrating injuries only.

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Nuclear Glucocorticoid Binding in Experimental and Human Leukemia*

JOHN STEVENS, M.D.†, Y.-W. STEVENS, M.S.†, JONATHAN RHODES, B.S.†, ESTELLE SLOAN, B.A.††, ROBERT L. ROSENTHAL, M.D.††, AND GERMAN STEINER, M.D.†††

Introduction

The glucocorticoids have occupied a prominent position in the treatment of leukemia and lymphoma for over a quarter of a century, first as single agents, and since the 1960's, in combination with other drugs (1). However, the precise mechanism of the antileukemic and lympholytic effect of the corticosteroids remains unknown. Furthermore, not all patients respond favorably to glucocorticoid administration and it is not clear why some patients who initially benefit from steroid therapy may become resistant to this form of treatment.

Exposure of corticoid-sensitive (CS) lymphocytes to glucocorticoids usually results in suppression of low molecular weight precursor uptake and incorporation into ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and proteins but there is no direct evidence that such effects mediate the killing action of the steroid (2). Glucocorticoid-induced nuclear damage has been attributed to intracellular accumulation of free fatty acids (3). Calcium may play a role in glucocorticoid-induced dissolution of some classes of lymphocytes, but not of others (4).

We have been using the CS and corticoid-resistant (CR) strains of mouse lymphoma P1798, a transplantable estrogen-induced thymoma, to study the mechanism of glucocorticoid action on CS tumor lymphocytes and to understand the basis for resistance in CR cells (5). CS P1798 regresses dramatically when tumor-bearing animals are injected with pharmacological doses of cortisol, whereas growth of the CR tumor is unaffected (6). Response of CS P1798 lymphocytes to glucocorticoids can also be demonstrated in vitro, indicating that hormone effects are exerted directly on the tumor cells. Thus, incubation of freshly isolated CS P1798 lymphocytes with 1μM cortisol results, within two hr, in marked suppression of ^{3}H-uridine uptake and incorporation into RNA (6). Cell death and dissolution are clearly evident by three to four hours (7). No such effects are observed with cell suspensions from CR P1798.

Contrary to the suggestion that catabolic effects of cortisol on CS P1798 lymphocytes were triggered by hormone suppression of glucose uptake, we were able to demonstrate cortisol inhibition of ^{3}H-uridine utilization by the tumor lymphocytes without a concomitant decrease of ^{14}C-deoxyglucose entry into the cells (6, 8). In addition, we found that the magnitude of cortisol-induced dissolution of CS P1798 lymphocytes was identical whether cells were exposed to steroid in complete tissue culture medium, or in medium from which glucose and pyruvate had been omitted (7).

In other studies, we have provided evidence that cortisol inhibition of uridine uptake by CS P1798 lymphocytes was preceded by sequential irreversible actinomycin D-sensitive and cycloheximide-sensitive steps (9). One interpretation, but by no means the only interpretation of these results, is that glucocorticoid action on tumor lymphocytes may be mediated by specific transcriptional and translational events. Whether the striking differences in cell surface properties between CS and CR P1798 tumor lymphocytes (prominent coat of Alcian blue-staining material on CS cells but not on CR cells, and decreased number of insulin binding sites on CR cells) are related to sensitivity or resistance to glucocorticoids remains to be established (10, 11).

It is currently believed that the initial steps in steroid hormone action are binding of the steroid to specific intracellular receptors, followed by translocation of the resulting hormone-receptor (HR) complexes to the nucleus, where they apparently set in motion the chain of events that culminates in phenotypic expression of the hormone effect (12). This model predicts that receptor-negative lymphocytes, or lymphocytes with receptors

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From the: † Research Institute, †† Department of Medicine, ††† Department of Laboratories, Hospital for Joint Diseases and Medical Center, New York, N.Y. 10035.

Request for reprints should be sent to J. Stevens, M.D., Research Institute of the Hospital for Joint Diseases & Medical Center, 1919 Madison Avenue, New York, N.Y. 10035.

that fail to bind to the nucleus after they have complexed with an active glucocorticoid will be glucocorticoid-resistant. So far, there has been no exception to this prediction. The early work of Hollander and Chiu showed that CR P1798 contained about half the number of cytoplasmic glucocorticoid binding sites as the CS strain of tumor (13). However, this reduction in binding capacity does not seem sufficient to account for the lack of response of the CR tumor to glucocorticoid administration.

In this article we will review our recent studies on glucocorticoid binding in the mouse lymphoma P1798 system and in peripheral lymphocytes of patients with chronic lymphatic leukemia (CLL). We will show that nuclear glucocorticoid binding properties in CR P1798 lymphocytes are quite different from those observed in CS P1798 tumor cells. In addition, we will provide evidence that nuclear glucocorticoid binding in CLL lymphocytes shares many of the characteristics of nuclear binding found in CS P1798 lymphocytes, consistent with the well documented steroid sensitivity of CLL cells (14–17).

Materials and Methods

The methods for measuring nuclear glucocorticoid binding in P1798 tumor cells and in freshly isolated peripheral blood lymphocytes from patients with CLL have been described in detail elsewhere and are summarized in the legends to the figures (18, 19). We chose ^{3}H-triamcinolone acetonide (^{3}H-TA) as the ligand for measuring glucocorticoid binding for two reasons. First, this potent synthetic glucocorticoid maximally stabilizes lymphoid glucocorticoid receptors (20, 21). Secondly, studies with ^{3}H-TA are not complicated by interaction of the hormone with plasma transcortin that could be present as a contaminant of the cell preparations. Transcortin binds cortisol with high affinity but has low affinity for the synthetic, fluorinated glucocorticoid, triamcinolone (22). We have verified experimentally that TA does not compete with ^{3}H-cortisol for binding to human or mouse plasma transcortin (19).

Results

Nuclear glucocorticoid binding in CS and CR P1798 tumor lymphocytes

Stabilization of the nuclear ^{3}H-TA binding component by carbobenzoxy-L-phenylalanine (CBZ-L-phe).

Figure 1 shows that incubation of P1798 lymphocytes with ^{3}H-TA at 37° resulted in substantial accumulation of ^{3}H-steroid in the nucleus of both CS and CR cells. At saturation about twice as much ^{3}H-TA was associated with purified CS nuclei than with purified CR nuclei. As

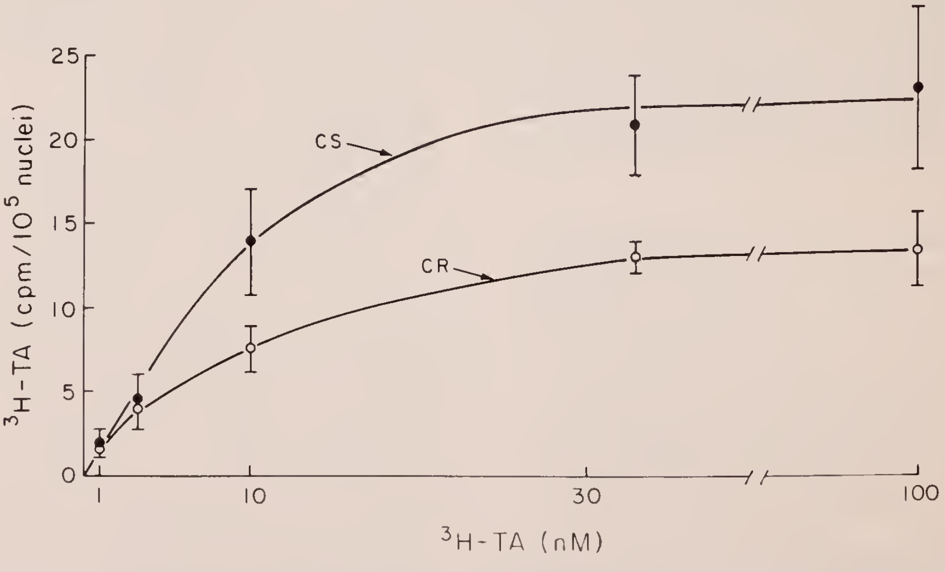

FIG. 1. Steroid concentration dependence of nuclear ^{3}H-TA uptake by P1978 tumor lymphocytes. CS and CR P1798 tumor cell suspensions were prepared as described previously, except that the Dulbecco's modified Eagle's medium was supplemented with 0.12% methylcellulose (15 centipoises). The cells were incubated for one hr at 37° under 95% air-5% CO_2 in the presence of varying concentrations of ^{3}H-TA alone, or ^{3}H-TA plus a 100 fold excess of nonradioactive TA. All subsequent steps were performed at 4° unless indicated otherwise. The cells were washed twice with steroid-free medium and purified nuclei prepared by homogenizing the cells in 2.0M sucrose containing 0.11% Triton X-100. The nuclei were extracted overnight at room temperature with absolute ethanol and the amount of radioactivity in the ethanol extract was counted with 33% efficiency. The results shown in this and subsequent Figures correspond to specific nuclear uptake of ^{3}H-TA; that is, the amount of radioactivity associated with nuclei from cells that had been incubated with ^{3}H-TA alone minus the amount of radioactivity associated with the nuclei of a parallel sample of cells that had been incubated with the same concentration of ^{3}H-TA plus a 100 fold excess of nonradioactive TA. Each point represents the mean ± S.D. of three separate experiments with each strain of tumor.

illustrated in Figure 2, steady state levels of nuclear-associated ^{3}H-TA were reached after 60 minutes incubation at 37° and were maintained for at least one more hour. Figure 3 shows that 90% to 95% of nuclear-associated radioactivity could be extracted from both CS and CR nuclei with 0.6M KCl. Surprisingly, only 15% to 25% of the ^{3}H-TA in the KCl extract was bound to macromolecules as judged by gel filtration on columns of Sephadex G25. This was not due to large amounts of free ^{3}H-TA in the purified nuclei. Instead, the low level of bound steroid in the 0.6M KCl extract resulted from dissociation of ^{3}H-TA from, or degradation of, the nuclear glucocorticoid binding component. Figure 4 shows that the loss of binding could be prevented by including the chymotrypsin inhibitor, CBZ-L-phe in the 0.6M KCl extraction buffer (23). At the optimal concentration of 10 mM CBZ-L-phe (identical for both strains of tumor), 70% of ^{3}H-TA in 0.6M KCl extracts from CS nuclei and 80% of the ^{3}H-TA in 0.6M KCl extracts from CR nuclei, was bound to macromolecules. The fraction of bound radioactivity in the 0.6M KCl-10mM CBZ-L-phe extracts was equivalent to 3900 ± 650 molecules of ^{3}H-TA/CR nucleus ($n = 18$) compared to 6100 ± 1560 molecules of bound ^{3}H-TA/CS nucleus ($n = 33$), a highly significant difference ($p < 0.001$). However, these values must be regarded as underestimates, since we have recently been able to increase the fraction of bound ^{3}H-TA in the 0.6M KCl-10mM CBZ-L-phe extracts of CS and CR nuclei to more than 90% by supplementing the extraction buffer with 0.2% bovine serum albumin and 10% glycerol.

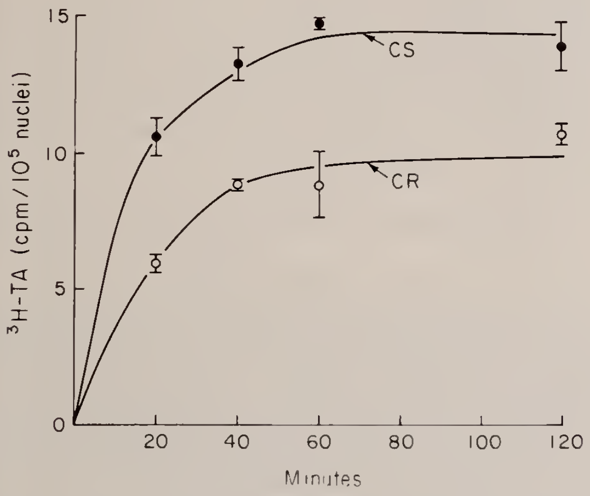

FIG. 2. Kinetics of nuclear ^{3}H-TA uptake by P1798 tumor lymphocytes. Tumor cell suspensions were incubated for the indicated periods of time at 37° with 10nM ^{3}H-TA after which nuclear-associated radioactivity was measured as in Fig. 1. Each point represents the average and range of two separate experiments with each strain of tumor.

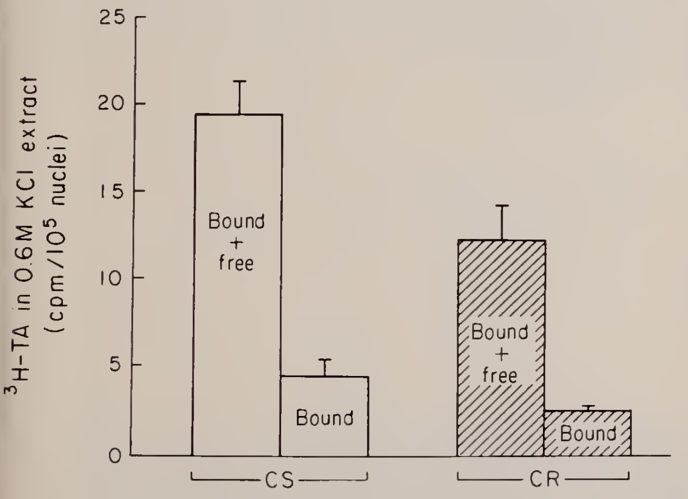

FIG. 3. Fraction of bound ^{3}H-TA in 0.6M KCl nuclear extracts of P1798 tumor lymphocytes, obtained in the absence of a protease inhibitor. Nuclei were isolated from CS and CR P1798 tumor lymphocytes that had been incubated for one hr at 37° with 30nM ^{3}H-TA. The nuclei were extracted with 0.6M KCl at 4° after which they were centrifuged at 27,000 × g for 15 minutes. The amount of ^{3}H-TA extracted with 0.6M KCl was determined by counting an aliquot of the 27,000 × g supernatant. Bound + free: total amount of ^{3}H-TA in the 27,000 × g (0.6M KCl) supernatant. Bound: portion of ^{3}H-TA in the 0.6M KCl extract that was associated with macromolecules as judged by gel filtration of the 27,000 × g supernatant on columns of Sephadex G25.

Differential extraction of ^{3}H-TA from CS and CR P1798 nuclei with monovalent, divalent and polyvalent cations.

Figure 5 shows that a significantly higher percentage of ^{3}H-TA was extracted from CS P1798 nuclei with 0.1M KCl than from CR nuclei ($p < 0.025$). Also shown is that the combination of 0.1M KCl with CBZ-L-phe was twice as effective as 0.1M KCl alone in extracting ^{3}H-TA from both types of nucleus ($p < 0.001$). These results suggest that the mode of ^{3}H-TA association with CS nuclei differs

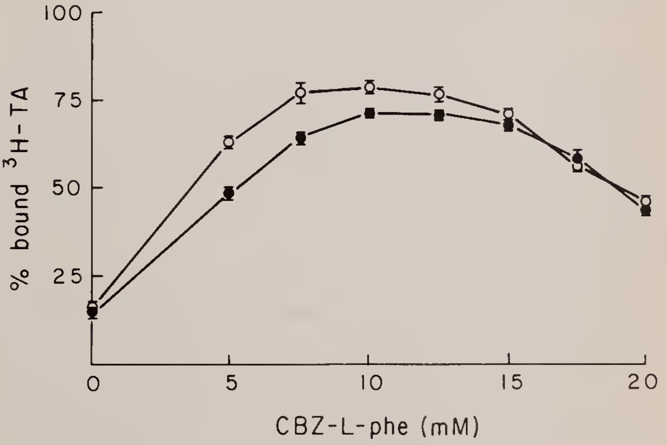

FIG. 4. Protective effect of CBZ-L-phe on the nuclear ^{3}H-TA binding component of P1798 tumor lymphocytes. Purified CS (●) and CR (○) P1798 tumor nuclei, isolated from cells that had been incubated with 30nM ^{3}H-TA for one hr at 37°, were extracted with 0.6M KCl plus the indicated concentrations of CBZ-L-phe. The percentage of bound ^{3}H-TA in the 0.6M KCl extracts was evaluated by gel filtration on columns of Sephadex G25. Two experiments were performed with each strain of tumor. (Reprinted with permission from reference 18).

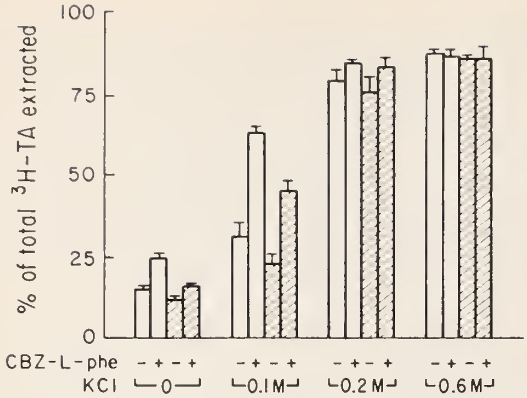

FIG. 5. Influence of KCl concentration on extractability of nuclear-associated ^{3}H-TA. Purified nuclei were isolated from CS (open bars) and CR (shaded bars) P1798 tumor lymphocytes that had been incubated with 30nM ^{3}H-TA for one hr at 37° after which the nuclei were extracted with the indicated concentrations of KCl in the absence or presence of 10mM CBZ-L-phe. The amount of bound plus free radioactivity in the KCl extracts is expressed as a percentage of total radioactivity (bound plus free salt-extractable counts plus KCl-resistant, ethanol extractable counts) associated with the nuclei. Each bar represents the mean ± S.D. of three to five experiments. (Reprinted with permission from reference 18).

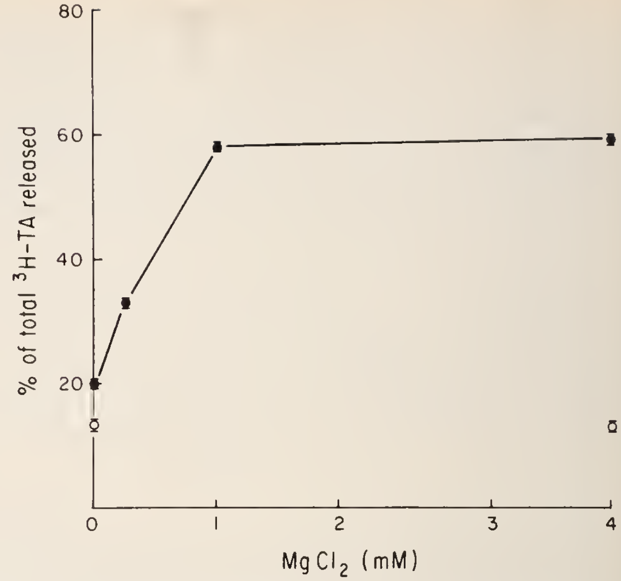

FIG. 6. MgCl$_2$-induced release of ^{3}H-TA from P1798 tumor lymphocyte nuclei. Nuclei, isolated from CS (●) and CR (○) P1798 tumor lymphocytes that had been labelled with 30nM ^{3}H-TA for one hr at 37°, were extracted with the indicated concentrations of MgCl$_2$. The 2.0M sucrose used for purifying the nuclei contained CaCl$_2$ instead of the usual MgCl$_2$, and the MgCl$_2$ extraction of the purified nuclei was performed in the presence of EGTA (ethyleneglycol-bis-(β-aminoethyl ether) N, N'-tetraacetic acid) to specifically chelate residual Ca^{2+}. The amount of ^{3}H-TA (bound + free) extracted by MgCl$_2$ is expressed as a percentage of total (MgCl$_2$-extractable plus MgCl$_2$-resistant, ethanol extractable) nuclear-associated ^{3}H-TA. Each point represents the mean ± S.D. of three experiments with each strain of tumor. (Reprinted with permission from reference 18).

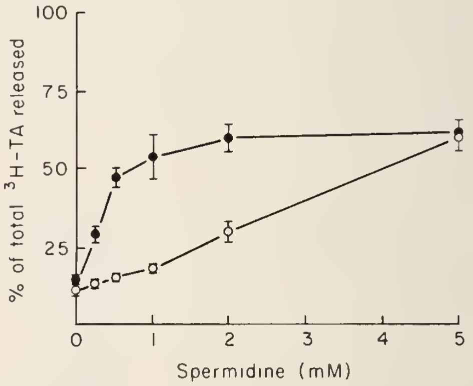

FIG. 7. Spermidine-induced release of ^{3}H-TA from P1798 tumor lymphocyte nuclei. Experimental details as in Fig. 6, except that the 2.0M sucrose used for purifying the nuclei contained MgCl$_2$. The spermidine extractions were performed in the presence of EDTA to chelate residual Mg^{2+}. Each point represents the mean ± S.D. of three to four experiments. (Reprinted with permission from reference 18.)

from that observed in CR nuclei. This difference could be demonstrated more dramatically when nuclei were extracted with divalent (Mg^{2+}) or polyvalent (spermidine) cations.

As illustrated in Fig. 6, millimolar concentrations of MgCl$_2$ extracted 60% of ^{3}H-TA from CS P1798 nuclei, whereas the amount of ^{3}H-TA extracted from CR nuclei was not significantly greater than that released with Mg^{2+} free buffer alone. Results obtained with spermidine are depicted in Fig. 7. Clearly, low concentrations of the polyamine extracted ^{3}H-TA from CS nuclei much more readily than from CR nuclei.

Even though extractions with MgCl$_2$ and spermidine were performed in the absence of the protease inhibitor CBZ-L-phe, 60 to 70% of the ^{3}H-TA released was bound to macromolecules, and over 90% was bound when 0.2% bovine serum albumin was added to the extraction buffer. This is consistent with the observation that chromatin-associated proteases are less active in low ionic strength media (24).

In experiments that have been described in detail elsewhere we found that neither the rate nor the magnitude of Mg^{2+}-induced release of ^{3}H-TA from CS nuclei were increased when extraction was performed at 20° instead of 4° (18). Similarly, release of ^{3}H-TA from CS and CR nuclei with 5mM spermidine was not influenced by raising the extraction temperature. These results argue against involvement of an enzymatic mechanism, assuming that diffusion of ^{3}H-steroid out of the nucleus is not a rate-limiting factor.

When labelled CS nuclei were mixed with unlabelled CR nuclei (or vice versa) and the mixtures of nuclei were extracted with 4mM MgCl$_2$ or 1mM spermidine, the amount of ^{3}H-TA released was that expected from the labelled nuclei alone. These mixing experiments appear to rule out the presence of diffusable releasing activity in CS nuclei that is capable of acting on CR nuclei, and of diffusable inhibitory activity in CR nuclei.

Nuclear glucocorticoid binding in human leukemic lymphocytes

Kinetics of nuclear uptake of ^{3}H-TA by CLL lymphocytes in Fig. 8 shows that incubation of CLL cells with ^{3}H-TA at 37° resulted in rapid association of steroid with the nucleus. Steady state levels of nuclear-associated ^{3}H-TA were maintained for at least two hr and were quite similar to those observed in a parallel sample of cells that had been exposed to ^{3}H-steroid at 24°, thus demonstrating the stability of the system at physiological temperature. Nuclear uptake of ^{3}H-TA was dependent on the extracellular concentration of steroid, and, as shown in Figure 9, maximal levels of nuclear-associated ^{3}H-TA were achieved when the cells were exposed to 10 to 50nM ^{3}H-TA.

Isolation and stabilization of the nuclear ^{3}H-TA binding component.

Extraction of purified CLL nuclei with 0.6M KCl released 90% or more of nuclear-associated ^{3}H-TA. In the absence of KCl, 10% or less of ^{3}H-TA could be extracted. As described above for mouse lymphoma P1798, only a small percentage (10% to 15%) of radioactivity in the 0.6M KCl extract was bound to macromolecules when extractions were performed in the absence of CBZ-L-phe (Fig. 10). As in the P1798 lymphocytes, CBZ-L-phe was quite effective in preventing breakdown of the CLL nuclear ^{3}H-TA binding component. Figure 11 shows that approximately 60% of ^{3}H-TA in the 0.6M KCl extracts was associated with macromolecules when 5 to 10mM CBZ-L-phe was included in the extraction buffer. This value could be increased to about 90% by performing the extractions in the presence of 1% bovine serum albumin and 10% glycerol, in addition to the CBZ-L-phe. Hence, the previously reported level of 1800 to 2500 molecules of bound ^{3}H-TA/CLL nucleus is obviously an underestimate (19).

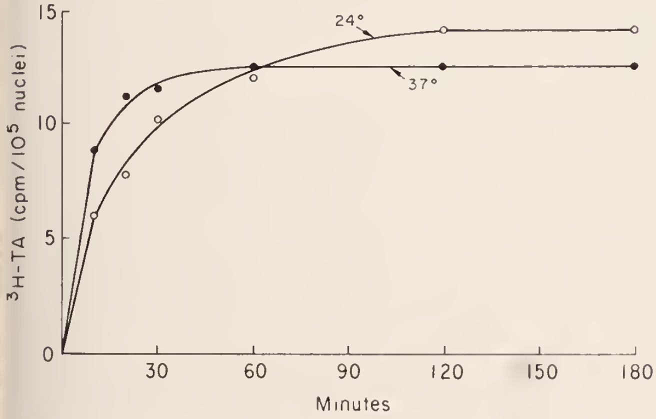

FIG. 8. Kinetics of ^{3}H-TA association with the nucleus in CLL lymphocytes. Peripheral lymphocytes from patient L.B. were divided into two portions. One portion was incubated at 24° and the other at 37°, for the indicated periods of time with 10nM ^{3}H-TA in RPMI-1640 medium supplemented with 25mM Hepes and 0.12% methylcellulose (15 centipoises) under 95% air-5% CO_2. Levels of nuclear-associated ^{3}H-TA were measured as described in Fig. 1. Similar results were obtained with cells from patient E.F. (Reprinted from reference 19, p. 97, courtesy of Marcel Dekker, Inc.).

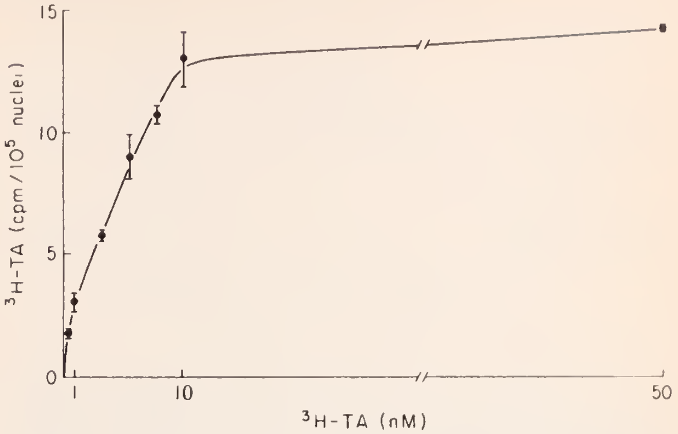

FIG. 9. Steroid concentration dependence of ^{3}H-TA association with the nucleus in CLL lymphocytes. Lymphocytes were incubated for 60 minutes at 37° with varying concentrations of ^{3}H-TA as described in Fig. 8. Levels of nuclear-associated ^{3}H-TA were measured as described in Fig. 1. Each point represents the mean ± S.E. of three experiments with three different patients. (Reprinted from reference 19, p. 99, courtesy of Marcel Dekker, Inc.).

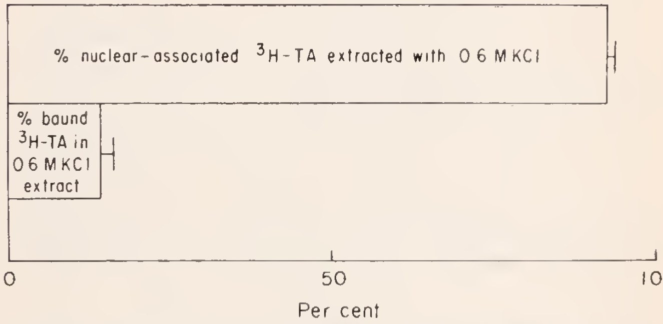

FIG. 10. Fraction of bound ^{3}H-TA in 0.6M KCl extracts of CLL lymphocytes nuclei, obtained in the absence of CBZ-L-phe. Nuclei were isolated from CLL lymphocytes that had been labelled for one hr with 10nM ^{3}H-TA as in Fig. 8. Extraction of the purified nuclei with 0.6M KCl, and other experimental details as in Fig. 3.

In other experiments we have shown that binding of ^{3}H-TA by CLL lymphocyte nuclei under whole cell conditions at 37° is specific for active glucocorticoids and is not due to contamination of the cells with plasma transcortin (19). We have found no obvious correlation between levels of nuclear-associated ^{3}H-TA, number of circulating lymphocytes and surface characteristics of the isolated lymphocytes as indicated by their ability to form E (spontaneous) or EAC (erythrocyte-antibody-complement) rosettes with sheep erythrocytes.

Extraction of nuclear-associated ^{3}H-TA with $MgCl_2$ and spermidine.

In view of the effectiveness of low concentrations of $MgCl_2$ and spermidine in releasing ^{3}H-TA from CS but

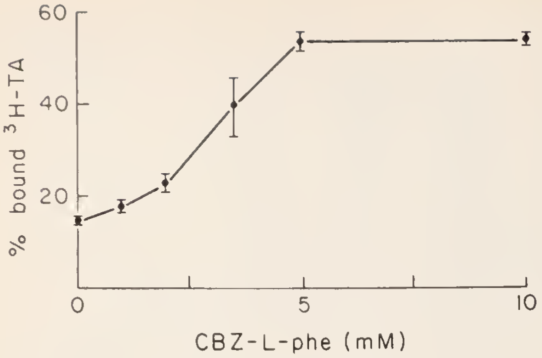

FIG. 11. Stabilization of the nuclear-associated ^{3}H-TA binding component of CLL lymphocytes by CBZ-L-phe. Nuclei, isolated from CLL lymphocytes that had been labelled with 10nM ^{3}H-TA, were extracted with 0.6M KCl plus the indicated concentrations of CBZ-L-phe. Bound ^{3}H-TA in the KCl extracts was determined by gel filtration of columns of Sephadex G25. Each point represents the average and range of two experiments with two different patients. (Reprinted from reference 19, p. 100, courtesy of Marcel Dekker, Inc.).

not from CR P1798 lymphocyte nuclei, it was of interest to determine the effect of these cations on nuclear-associated ^{3}H-TA in CLL lymphocytes. Lymphocytes from each patient were divided into two portions. One portion of cells was used to assess sensitivity of the lymphocytes to glucocorticoids by monitoring the effect of nonradioactive TA on ^{3}H-uridine incorporation into acid-insoluble materal. The other portion of cells was incubated with 10nM ^{3}H-TA for 60 minutes at 37°, the nuclei were isolated and the ability of 4mM $MgCl_2$ or 1mM spermidine to release ^{3}H-TA from the purified nuclei was examined. This type of study was performed in ten patients.

As reported briefly elsewhere, $MgCl_2$ and spermidine extracted substantial amounts (50% to 70%) of nuclear-associated ^{3}H-TA from lymphocytes of all ten patients (25). In addition, the lymphocytes from these patients were corticoid-sensitive, as indicated by the ability of TA to suppress utilization of ^{3}H-uridine by the cells. After four hr exposure to ten or 100nM TA at 37°, incorporation of ^{3}H-uridine into acid-insoluble material was reduced by 42% (range: 24%–57%) and was nearly maximal with 10nM TA. Interestingly, this is the same concentration of TA required for achieving close to maximal levels of nuclear glucocorticoid binding under intact cell conditions at physiological temperature.

Discussion

In this paper, we report on striking differences in nuclear glucocorticoid binding between CS and CR P1798 (mouse) tumor lymphocytes and describe a reliable procedure for isolating specific glucocorticoid binding components from purified human and murine leukemic lymphocyte nuclei. Since nuclear glucocorticoid binding was allowed to take place under whole cell conditions at 37°, we have circumvented some of the difficulties involved in interpreting results obtained with "cell-free" nuclear binding systems at nonphysiological temperatures.

Our finding that low concentrations of monovalent, divalent, and polyvalent cations extracted significantly higher percentages of ^{3}H-TA from nuclei of CS P1798 lymphocytes than from CR nuclei suggests that interaction of the glucocorticoid binding component with the nucleus may be weaker in the CS lymphocytes. Extraction of purified CLL nuclei with millimolar concentrations of $MgCl_2$ and spermidine also resulted in considerable release of macromolecule-bound, nuclear-associated ^{3}H-TA. Inasmuch as the CLL lymphocytes used for these studies were glucocorticoid-responsive (as judged by the ability of TA to suppress uridine utilization by the cells), it is tempting to speculate that facile release of nuclear-associated ^{3}H-TA by divalent cations and polyamines may be a general property of CS lymphocytes and not just a peculiarity of the CS P1798 tumor. However, many CS and CR variants will have to be screened before a definitive statement can be made.

The nature of the site which glucocorticoid binding component(s) interact with in the nucleus is still unknown. DNA appears to play an important role but it is equally clear that other nuclear constituents such as the acidic or basic nuclear proteins, ribonucleoprotein particles or the nuclear membrane may also be involved (26). Since divalent cations and polyamines bind to the phosphate groups on DNA, the $MgCl_2$ and spermidine-induced release of ^{3}H-TA from tumor lymphocyte nuclei may be due to displacement of the ^{3}H-TA binding component from negatively charged groups on chromatin (27).

A major question to be resolved is whether the difference in the mode of ^{3}H-TA interaction with the nucleus between CS and CR P1798 tumor lymphocytes is due to differences in the glucocorticoid binding component, to differences at the nuclear level, or to both. In order to obtain a complete answer to this question, it will be necessary to develop a cell-free nuclear binding system that preserves all the characteristics of the nuclear binding process as it occurs in the intact cell. In addition, it will be necessary to undertake a detailed comparison of the physicochemical properties of purified cytoplasmic and nuclear glucocorticoid binding components from CS and CR lymphocytes. The feasibility of such a study depends in part on whether the glucocorticoid binding component(s) can be sufficiently stabilized to withstand the purification procedure. Our ability to reduce or prevent breakdown of nuclear ^{3}H-TA binding components by including CBZ-L-phe, bovine serum albumin and glycerol in the nuclear extraction buffer is an encouraging step in this direction.

Preliminary experiments suggest that the physicochemical properties of the nuclear ^{3}H-TA binding component from CS P1798 lymphocytes are quite different from those of the ^{3}H-TA binding component isolated from CR P1798 nuclei. The nuclear ^{3}H-TA binding component from CLL lymphocytes appears to resemble the CS P1798 nuclear glucocorticoid binding component, when analyzed by agarose gel filtration. This observation correlates with the glucocorticoid sensitivity (in vitro) of the CLL cells.

Further studies on lymphoid glucocorticoid receptors and their interaction with the nucleus should help to better understand how glucocorticoids cause dissolution of CS lymphocytes and hopefully will shed new light on the mechanism of resistance in receptor-positive cells that are nonresponsive to steroid.

Summary

Nuclear glucocorticoid binding was studied in lymphocytes from the corticoid-sensitive (CS) and corticoid-resistant (CR) strains of mouse lymphoma P1798. Purified nuclei, isolated from cells that had been incubated at 37° with ^{3}H-triamcinolone acetonide (^{3}H-TA) were extracted with monovalent (KCl), divalent (Mg^{2+}) or polyvalent (spermidine) cations. Breakdown of glucocorticoid binding components during extraction of nuclei with KCl was prevented by inclusion of the chymotrypsin inhibitor carbobenzoxy-L-phenylalanine (CBZ-L-phe) in the extraction buffer. Levels of macromolecule-associated ^{3}H-TA were 2 to 2.5 fold higher in CS P1798 nuclei than in nuclei from CR P1798 tumor lymphocytes. Low concentrations of KCl, $MgCl_2$ and spermidine extracted significantly higher percentages of ^{3}H-TA from CS nuclei than from CR P1798 nuclei, which suggested that interaction of the ^{3}H-TA binding component with the nucleus might be weaker in the CS cells. Nuclear binding of ^{3}H-TA was also demonstrated in freshly isolated, peripheral blood lymphocytes from 14/14 patients with untreated chronic lymphatic leukemia (CLL). CBZ-L-phe was also required to prevent degradation of the binding component when the CLL nuclei were extracted with 0.6M KCl. As in the CS P1798 mouse tumor lymphocytes, millimolar concentrations of $MgCl_2$ and spermidine readily extracted a substantial portion of macromolecule-associated ^{3}H-TA from the purified CLL nuclei. This result correlates with the glucocorticoid sensitivity of the CLL lymphocytes, as measured by TA-induced suppression of ^{3}H-uridine utilization in vitro.

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Progesterone and Breast Cancer*

EDWARD J. DIAMOND, Ph.D. and VINCENT P. HOLLANDER, M.D.

Introduction

The involvement of endocrine factors in the genesis and growth control of mammary cancer has long been appreciated. A review of recent studies reinforces the belief that the pituitary gland and ovarian secretions influence experimental and human mammary cancers (1–4).

There is little doubt that at physiologic concentrations, estrogens can stimulate growth of at least some mammary cancers, although the mechanism by which this stimulation is carried out is not completely understood (1, 3, 5, 6). In contrast, the role of progesterone in breast cancer is much less clear. Confusing literature attests to this; progesterone has been shown to stimulate as well as to inhibit rat mammary tumor growth, to act as a cocarcinogen, and has been used as a therapeutic agent (7–13, 15–18). An excellent review has recently appeared that leaves little doubt that progesterone plays a definite rôle in breast cancer (19).

In the present report we shall attempt to review what is currently known about the role of progesterone in both human and animal breast cancer, and to describe studies carried out in our laboratory on the endocrine control of growth and regression using the hormone responsive rat mammary tumor, MTW9. We shall describe the endocrine requirements for growth of MTW9 with special emphasis on some recently discovered effects of progesterone. We will show why the MTW9 mammary tumor system is a suitable model for human breast cancer.

Effects of Progesterone in Human and Animal Breast Cancer

Stimulatory Effects: Early studies that followed development of the dimethylbenzanthracene (DMBA)-induced rat mammary tumor by Huggins and coworkers showed that progesterone, under the appropriate experimental conditions, enhanced DMBA mammary tumorigenesis. Progesterone administered to intact rats previously given DMBA stimulated tumor growth, accelerated tumor appearance and increased the number of tumors. Mammary tumor formation was also stimulated by progesterone in ovariectomized rats (7, 20, 21). Similar findings were reported by Jabara after implantation of progesterone pellets into rats shortly after DMBA administration (8).

Recently, progesterone has been shown to stimulate in vivo DNA synthesis in a pregnancy-dependent mouse mammary tumor while no effect on plasma prolactin (PRL) concentrations was observed (9). Administration of estradiol alone or estradiol plus progesterone increased plasma PRL; estradiol alone had no effect on DNA synthesis while estradiol plus progesterone did not stimulate DNA synthesis anymore than with progesterone alone. Human placental lactogen alone was not stimulatory in this system but when combined with progesterone showed greater stimulation of DNA synthesis than with progesterone treatment alone, suggesting that a synergism exists between the two hormones (9). These findings are of interest because PRL is believed to be an important endocrine growth factor in rodent mammary tumorigenesis (22–24). However, for this tumor strain, progesterone is more important for tumor growth than either estradiol or a lactogenic hormone. Progesterone appears to be required for tumor stimulation with a lactogenic hormone.

Progesterone has also been reported to be a potent cocarcinogen in mice; it has been shown to enhance mammary gland carcinogenesis induced by both viral and chemical agents and to increase the incidence of prolactin-induced mouse mammary tumors (14, 25).

Pregnancy and pseudopregnancy, two physiologic states associated with increased progestational activity, enhanced the growth of carcinogen-induced mammary tumors and caused the appearance of new tumors (12, 17, 26–28). When hormonal stimulation was rapidly terminated by parturition, tumor regression occurred (12). The endocrine factor that stimulates growth of carcinogen-induced mammary tumors during pregnancy is probably placental lactogen (29). When intact DMBA-treated

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From the Research Institute of the Hospital for Joint Diseases and Medical Center, New York, N.Y. 10035.

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Requests for reprints should be sent to E. J. Diamond, Ph.D., Research Institute of the Hospital for Joint Diseases and Medical Center, 1919 Madison Avenue, New York, N.Y. 10035.

rats received daily injections of human placental lactogen (HPL), appearance and growth of mammary tumors were stimulated. In contrast, growth of mammary tumors in ovariectomized-adrenalectomized rats treated with HPL were stimulated for only ten days; thereafter, tumor growth slowed down in spite of continued treatment with HPL, suggesting that steroids were required for continued growth stimulation. The intact HPL-treated rats showed evidence indicative of a luteotropic effect of HPL (continuous diestrus vaginal smear and functional corpora lutea). The study suggests that it may be placental lactogen that stimulates tumor growth during pregnancy by a direct effect on the tumor, and indirectly on the ovaries by enhancing progesterone secretion through its luteotropic effect (29).

PRL is probably the principal hormonal growth factor in carcinogen-induced rat mammary cancers (4, 22, 24). However, PRL by itself is not able to maintain tumor growth. Several studies show that ovarian hormones, especially progesterone, are required to stimulate or maintain mammary tumor growth by PRL (30–32).

Stimulation of DMBA tumor growth occurs during lactation and is dependent upon the presence and intensity of the suckling stimulus. If suckling is prevented, tumor regression occurs, suggesting that PRL is responsible for stimulation of tumor growth during lactation (26, 30, 33). However, ovariectomy during lactation blocked the stimulatory effect of suckling on tumor growth, and daily injections of progesterone were able to overcome the inhibitory effect of ovariectomy (30). Ovariectomy also inhibits tumor growth elicited by daily injections of PRL in nonlactating postpartum rats (30). These findings demonstrate that an elevated level of PRL by itself is unable to maintain tumor growth and implies that either progesterone is required for PRL-stimulated mammary tumor growth or progesterone alone is responsible for tumor growth in the lactating rat. Elevated levels of progesterone are controlled by PRL in the lactating rat (34).

When DMBA-induced mammary tumor bearing rats were ovariectomized and serum PRL increased by placing lesions in the median eminence of the hypothalamus, the mammary tumors grew for 10–12 days and then regressed in spite of a high serum PRL (240 ng/ml) (31, 32). Again, elevated PRL was not able to sustain mammary tumor growth in the absence of the ovaries. Depletion of some ovarian factor, perhaps progesterone must be responsible for mammary tumor regression under these circumstances. Progesterone may be required to maintain mammary tumor growth–PRL may simply stimulate ovarian progesterone secretion. However, there is evidence that argues against this concept. Examination of surviving ovaries grafted into ovariectomized rats with median eminence lesions (serum PRL elevated) failed to show any functioning corpora lutea indicating that another ovarian product may have been responsible for continued tumor growth (31).

The question of what mammary tumors are deprived of after ovariectomy has also been studied. DMBA tumor growth can be restored after ovariectomy either by administration of progesterone or estradiol and by combinations of both steroids (35, 36). Tumor reactivation after ovariectomy was greater when progesterone was administered with estradiol (90%) than when estradiol was given alone (50%) (36).

The studies described so far do not explain how progesterone elicits its stimulatory effect on rodent mammary tumor induction and growth, but they clearly demonstrate that it plays an important physiological role.

Inhibitory Effects: The progestational state may protect the mammary gland from the effects of carcinogens. When mammary glands of rats are stimulated either by pregnancy or with pituitary or ovarian hormones they become much less responsive to the action of carcinogens (10, 12, 13). Progesterone injections protected rats from mammary tumors induced by the synergistic effect of estrogen and radiation (11). When progesterone was injected into rats 20 days before DMBA administration, it rapidly stimulated the mammary epithelium and the incidence of mammary tumor induction was greatly reduced (13). Welsch and coworkers showed that progesterone injections and transplantation of pituitary homografts before administration of DMBA enhanced growth of the mammary glands and greatly inhibited mammary tumor development. The pituitary grafts, free from hypothalamic inhibition of PRL secretion were believed to exert an inhibitory effect through the luteotropic action of PRL on the ovary (10, 37). When mammary glands are exposed to hormonal stimulation they become refractory to subsequent carcinogen action (12, 13). This appears to be due to rapid metabolism of the carcinogen by the stimulated mammary glands. The carcinogen is not present long enough to initiate tumor formation (38). Early pregnancy (and subsequent parturition) is known to exert a protective influence against breast cancer in women by decreasing the incidence of the disease (39). A critical period for initiation of mammary cancer, similar to that in the rat may also exist in women; the hormone-stimulated breast growth of an early pregnancy may be protective.

Progesterone may protect the mammary epithelium by opposing the action of estradiol which favors the development of carcinoma (40, 41). This hypothesis implies that persistent estrogenic stimulation accompanied by an inadequate progestational phase of the menstrual cycle may provide an environment favorable for the development of breast cancer.

Progesterone as a therapeutic agent: In contrast to its stimulatory effects on tumor growth, progesterone can cause tumor regression under the appropriate circumstances. Synthetic progestational agents have been used to treat advanced breast cancer in postmenopausal women (16–18).

Huggins and coworkers showed that progesterone, when combined with large doses of estradiol, could cause regression of DMBA-induced rat mammary tumors (7, 21). Pharmacologic doses of estrogens alone also cause mammary tumor regression and several clinical studies show that the addition of a progestational agent to the treatment regimen enhances the effect of high dose estrogen on tumor regression (42–45). Remissions after progestogen-estrogen combinations were higher than with progestogens alone. Some breast cancers that had not previously responded to estrogen therapy alone did so after treatment, with the combinations (4, 6, 15, 16). Stoll treated breast cancers in postmenopausal women with several progestational agents (15). When endogenous estrogen levels were high, as evidenced by vaginal cornification, the response to progestogen therapy was better than for patients with atropic vaginal smears. The combination of endogenous estrogen and progestational agents gave the better response. Some level of estrogen may be required for progesterone-induced tumor regression. It has been suggested that this may be because of the stimulatory effect of estrogen on progesterone receptor synthesis (19).

The mechanism(s) by which progestogens elicit tumor regression are not known. They may act indirectly by influencing pituitary secretion or be metabolized to more active steroids, or act directly on the tumor (16, 17). A direct action on the tumor is suggested by several reports of breast tumor regression in hypophysectomized patients (47, 48).

Progesterone Receptors: Progesterone receptors have been found in both normal and neoplastic tissues of several animal species and in humans (49). In estrogen sensitive tissues synthesis of progesterone receptor (PR) is increased by the action of estrogens while progesterone decreases the concentration of its own receptor (50–52). A single injection of estradiol can cause an eight-fold increase in PR within 24 hours while the administration of progesterone leads to a rapid decrease in PR (52). Estrogen regulation of PR probably acts at the target cell level and not via the pituitary, because PR levels are restored by estradiol and not by prolactin in adrenalectomized-ovariectomized-hypophysectomized rats (19).

The observation that PR is dependent on estrogen stimulation led to the suggestion that PR levels may indicate whether a breast tumor has a functional estradiol receptor system and therefore would still be under hormonal control (53). Failure of 40% of women with estradiol receptor positive breast tumors to respond to endocrine therapy may be because of a defect in the estradiol receptor system that occurs after the binding of estradiol to its cytosol receptor. PR is an end product of estrogenic stimulation and its presence would suggest a functional estradiol receptor system and hormone dependence (53). Recently, McGuire has reexamined this hypothesis by asking whether PR measurements have improved the selection for endocrine therapy (54). Patients with both receptors (estradiol and progesterone) show the best remission rates but some have estradiol receptor positive tumors and no measurable PR, yet still show a response to endocrine therapy. Additional studies are required before this hypothesis can be fully accepted.

Progesterone receptors are also present in DMBA-hormone-responsive mammary tumors and their levels also dependent on estrogenic stimulation. Experimental conditions such as ovariectomy or antiestrogen treatment that result in tumor regression decrease tumor PR levels (55, 56). A combination of estradiol and progesterone administered to ovariectomized rats with regressing DMBA tumors reversed tumor regression and increased PR while progesterone injections alone did not restore tumor growth, indicating that estradiol priming may be a prerequisite for the progestational response (55). The presence of progesterone receptors and their control by estrogen does not as yet explain the effects of progesterone in mammary cancer but does confirm the functional significance of progesterone in breast cancer.

Endocrine control of growth and regression of MTW9

MTW9 is a carcinogen-induced rat mammary carcinoma transplantable in female W/Fu rats (57, 58). Growth of MTW9 is stimulated by PRL. MTW9 rarely grows without elevated levels of serum PRL that are usually achieved by coimplantation with a pituitary mammosomatotropic tumor (MtT). MTW9-MtT denotes the mammary tumor MTW9 when it is coimplanted with a mammasomatotropic tumor (59, 60). The mammosomatotropic tumor, MtTW10 used in most of the studies to be described secretes large amounts of prolactin, growth hormone, and probably ACTH (61, 62).

Early studies showed that ovarian hormones as well as prolactin are required for growth of MTW9 (59). Ovariectomy (ovex) at the time of tumor implantation (MTW9 coimplanted with MtT) or shortly thereafter prevents mammary tumor growth. MtT growth is only slightly retarded by ovex, but its ability to secrete large amounts of PRL is not impaired by ovex (63). Injections of estradiol or progesterone or a combination of both steroids started at the time of tumor implantation restores growth of MTW9 in ovex rats. Table I shows that administration of estradiol and progesterone was able to replace the ovaries and resulted in growth of MTW9-MtT similar to that observed in intact rats. Progesterone or estradiol alone resulted in smaller tumors that appeared later. Inhibition of MTW9 growth in ovex rats is not due to PRL deficiency. MTW9 does not grow out

TABLE I

Effect of Ovarian Steroid Administration on Growth of MTW9-MtT in Ovariectomized** Rats*

Experimental Condition	Weight of MTW9 at Autopsy*** gms Tumor/100 gms b. wt.
intact	9.2 ± 1.3
ovex	0.1 ± 0.1
ovex + estradiol + progesterone	10.6 ± 1.7
ovex + estradiol	1.0 ± 0.3
ovex + progesterone	4.1 ± 0.1

* Rats bearing MTW9-MtT received daily injections of 10 μg estradiol or 3 mg of progesterone or a combination of both steroids.

** Rats were ovariectomized (ovex) on day of tumor implantation.

*** Autopsied on day 44. (Data from Macleod, Allen and Hollander, Reference 59)

when transplanted into ovex rats even when serum PRL is elevated by MtT (63). These studies show that both ovarian steroids are required for optimal growth of MTW9-MtT and that they act together with pituitary hormones (MtT). Ovarian steroids are probably involved in the initiation of growth of MTW9-MtT or are required for some early growth process.

Table I also shows that progesterone is required for growth. Greater tumor growth was achieved in ovex rats receiving only progesterone than in rats receiving only estradiol. These early studies indicated that progesterone, under the appropriate experimental conditions can stimulate growth of MTW9.

Ovarian hormones are also required for survival (viability) of MTW9-MtT. When MTW9-MtT is implanted into intact rats without an MtT, it does not grow but remains viable for long periods of time. Implantation of an MtT, 6–12 months thereafter elicits growth of MTW9. In contrast, MTW9 will not grow out 6–12 months later if implanted into ovex rats, even if at a later date estrogen, progesterone, and PRL (MtT) are given (unpublished observations). Ovarian steroids must be administered from the time of ovex to obtain growth of MTW9 at a later date, indicating that estrogen and progesterone are required also for tumor viability.

That MTW9-MtT requires elevated levels of serum PRL for growth can also be demonstrated by surgical removal of the MtT (MtT resection). Figure 1 shows that resection of MtT causes prompt regression of MTW9-MtT. Regression is accompanied by a rapid decline in serum PRL which returns to normal levels (60). The figure also shows that ovex does not lead to mammary tumor regression. Ovex of MTW9-MtT bearing rats usually results in cessation of growth but does not reduce the high levels of serum prolactin. This is an interesting observation, when it is recalled that early growth of MTW9-MtT requires ovarian steroids. When ovex is combined with MtT resection, regression of MTW9-MtT is more rapid and complete; most tumors are no longer palpable three weeks after surgery (Fig. 1). This observation suggests that the MtT exerts an inhibitory influence on ovex-induced tumor regression; MTW9-MtT responds to ovex when the MtT is removed.

Growth of MTW9 in perphenazine treated rats

Coimplantation of MTW9 with MtT is a convenient method for routinely growing MTW9, but it not only exposes the tumor to high levels of PRL, but to other hormonal abnormalities. Rats bearing MTW9-MtT do not live very long; rapid growth of the MtT kills most animals 50–60 days after tumor implantation. We demonstrated that MTW9 could be grown in rats with serum PRL increased by daily injections of the tranquilizing drug perphenazine (60). This is a convenient way of increasing serum prolactin and eliminating some of the hormonal abnormalities of MtT-bearing rats. It also extends the life span of the tumor-bearing rats.

MTW9 grown in perphenazine treated rats (now referred to as MTW9-P) although similar morphologically to the parent tumor, MTW9-MtT, shows important differences. Table II compares the properties of MTW9-MtT with MTW9-P. MTW9-MtT-bearing rats have much higher serum PRL concentrations (500–10,000ng/ml) than those with MTW9-P (250–800ng/ml). When perphenazine treatment is discontinued serum PRL returns to normal but the mammary tumor (now referred to as MTW9-PD) does not regress but remains stationary. In contrast, when serum PRL returns to normal after MtT resection MTW9-MtT regresses (Fig. 1). The most interesting difference between MTW9-MtT and MTW9-P is observed after ovex. MTW9-MtT does not

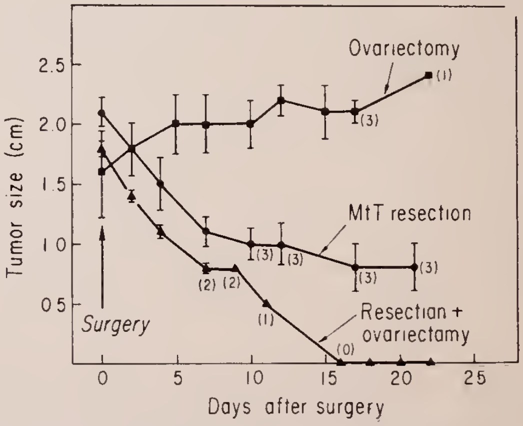

FIG. 1. *Effects of resection, ovariectomy and resection plus ovariectomy on growth of MTW9-MtT.* Rats bearing MTW9-MtT were subjected to MtT resection (filled circles), ovariectomy (squares), or ovariectomy + MtT resection (triangles) on day 0. Four animals were subjected to each surgical procedure. Tumors were measured at intervals noted. Numbers in parentheses indicate number of animals remaining with palpable tumor. In the ovariectomized group, one animal died by day 17 and three died by day 24. Tumor size is expressed as average diameter [(length + width)/2] (mean ± SE). Reprinted from Reference 60, by courtesy of Cancer Research.

regress after ovex (Fig. 1). Ovex of MTW9-P bearing rats causes striking tumor regression within 20 days. Some tumors show complete regression (60). When ovex is carried out in rats bearing MTW9-P and perphenazine administration continued serum PRL decreases as a result of ovex but it remains well above normal and at a concentration adequate for tumor growth. Under these conditions, significant tumor regression occurs after ovex. MTW9-PD, the tumor that remains after perphenazine treatment is stopped, also regresses after ovex. When MTW9-P has completely regressed (no longer palpable) it can be regrown if 5 to 10 μg of estradiol are administered daily. Growth of MTW9 in perphenazine-treated rats shows that a mammary tumor that regresses after ovex (MTW9-P) can be derived from a tumor (MTW9-MtT) that does not regress after ovex.

Both MTW9-MtT and MTW9-P have cytosol estradiol receptors (64, 65). When receptor studies were unable to explain the difference in response to ovex, we then looked for endocrine host factors to explain why MTW9-P and MTW9-PD regress after ovex and MTW9-MtT does not.

We believe that both mammary tumors are excellent models for the human disease; MTW9-MtT can be compared with breast cancers that contain estradiol receptor but do not regress after ovex. After MtT resection it is also a model for hypophysectomy-induced remission. MTW9-P models the human estradiol receptor positive breast cancer which regresses after ovex.

Why Doesn't MTW9-MtT Regress After Ovariectomy?

The question of why MTW9-MtT, a mammary tumor that contains estradiol receptor does not regress after ovex is an important one. If we understood the reason(s) for failure of mammary tumors to regress after ovex it might help us to understand why about 40% of women with estradiol receptor positive breast cancers do not respond to endocrine therapy (66). Some endocrine factor present in hosts of MTW9-MtT and not in those of MTW9-P may inhibit ovex-induced mammary tumor regression.

Although MTW9-MtT does not regress after ovex, it has the genetic information necessary for ovariectomy-induced regression, but it is inhibited by the presence of the MtT. Ovex alone does not cause regression of MTW9-MtT (Fig. 1). Resection of MtT results in regression. When ovex and resection are carried out together, MTW9-MtT regresses more rapidly and regression is almost always complete. This last observation suggested that the MtT secretes a substance that inhibits ovex-nduced regression. This result (that is, more rapid and complete mammary tumor regression after combined ovex and resection) could not have been obtained if there were genetic inability to respond to ovex.

If MtT produced estrogens either directly or indirectly, then lack of ovex-induced regression would be easily understood. The observations that rats bearing MtT do not manifest a normal estrus cycle but are pseudopregnant, have atropic uteri and have very low concentrations of serum estradiol suggests that the MtT does not secrete estrogens (67).

TABLE II

Properties of Mammary Tumors

	MTW9-MtT	MTW9-P
serum prolactin elevated by:	coimplantation with a mammosomatotropic tumor	daily perphenzine injections
serum prolactin levels achieved: (normal = 10–250 ng/ml)	500–10,000 ng/ml	250–800 ng/ml
ovariectomy:	no regression	regression
MtT resection:	regression	—
MtT resection + ovariectomy:	more rapid and complete regression	—
hormone binding (fm bd/mg prot)		
estradiol (cytosol)	48 ± 3	196 ± 29
prolactin (membrane)	2.9 ± 0.3	12.2 ± 1.3
possible relationship to human breast cancer:	1) hypophysectomy induced regression after MtT resection 2) ER+ mammary tumor does not regress after ovariectomy	1) ER+ mammary tumor that regresses after ovariectomy

We considered the possibility that MTW9-MtT failed to regress after ovex, not because it lacked the genetic machinery but because some hormonal abnormality in MtT-bearing rats prevented ovex-induced regression. Some of the known endocrine abnormalities of MtT-bearing rats are shown in Table III. Rats bearing MtT have elevated serum concentrations of prolactin, growth hormone, progesterone and corticosterone. The possibility that an endocrine abnormality prevented ovex-induced mammary tumor regression was tested by simulating the abnormal endocrine environment produced by MtT growth in rats bearing MTW9-PD (67). MTW9-PD are tumors grown in rats treated with perphenazine but after the drug has been discontinued, most tumors remain stationary, hosts manifest normal estrus cycles and have normal serum prolactin concentrations. The mammary tumor, MTW9-PD, regresses after ovex.

Table IV restates our hypothesis (that is, an endocrine abnormality in MtT bearers prevents ovex-induced tumor regression) and outlines our experimental approach. The endocrine environment of the MtT bearer was simulated in rats bearing MTW9-PD by daily hormone treatments of ACTH, a progestin, growth hormone and prolactin. After treatment for a given period of time,

TABLE III

Hormonal Environment of Rats Bearing Mammosomatotropic Tumors

Hormone	Serum Concentration		Reference
	+MtT	Control*	
prolactin	500–10,000 ng/ml	10–250 ng/ml	60
growth hormone	5400 ± 670** ng/ml	5.4–9.8 ng/ml	61
progesterone	34 ± 3.1** ng/ml	12.0 ± 1.3** ng/ml	67
corticosterone	33 ± 3.5** μg/100 ml	2.0 ± 1.5** μg/100 ml	67

* nontumor-bearing W/Fu female rats

** mean ± S.E.

TABLE IV

What Prevents Ovariectomy-Induced Regression of MTW9-MtT?

Working hypothesis: Some hormonal abnormality in MtT-bearing rats prevents ovariectomy-induced mammary tumor regression.

Experimental approach: simulate endocrine environment produced by MtT in rats bearing MTW9-PD.

MTW9-PD
↓ hormone treatment for 7–30 days
ovariectomy
continue hormone treatment → does hormone treatment prevent mammary tumor regression?

MTW9-PD tumor-bearing rats were ovariectomized and hormone treatments continued. Tumors were measured periodically to determine whether the particular treatment was able to prevent ovex-induced regression of MTW9-PD.

Table V shows how the endocrine environment of MtT bearing rats was simulated in hosts of MTW9-PD. Administration of ACTH, the long-acting progestational agent, hydroxyprogesterone caproate, growth hormone and implantation of the growth-hormone-secreting tumor, MtTW5-OM all failed to inhibit ovex-induced regression of MTW9-PD. The obvious explanation that high serum prolactin prevented ovex-induced regression in animals bearing MtT was also ruled out. Administration of 2, 4 and 12 mg of prolactin per day to rats bearing MTW9-PD stimulated growth of mammary glands and tumors and increased serum prolactin concentrations to levels found in hosts of MtT. In spite of the short half life reported for injected prolactin in the rat (68, 69), we have shown that chronic treatment with ovine prolactin slows down the hormones disappearance rate from blood. After a single 2 mg injection of ovine prolactin to chronically treated rats, the serum concentration of ovine prolactin exceeds levels produced by most mammosomatotropic tumors and persists over an 8-hour period. Hence, we were able, with multiple hormone injections to simulate the high prolactin levels produced by MtT; however, no inhibition of ovex-induced tumor regression was observed (67).

Table V shows that only implantation of an MtT prevented regression after ovex. MtT greatly stimulated mammary tumor (MTW9-PD) growth both before and after ovex. MtT may secrete a substance(s) that blocks ovex-induced regression or may inhibit ovex-induced regression of MTW9 by secreting a combination of prolactin, growth hormone and ACTH, although none of these hormones alone were able to inhibit regression of this tumor. When a high dose mixture of ACTH, prolactin and growth hormone was administered to a limited number of rats it produced rapid tumor growth and extreme mammary gland stimulation, but also failed to inhibit tumor regression (Table V).

We were unable to demonstrate inhibition of ovex-induced mammary tumor regression by administration of any of the known secretory products of MtT. Either MtT directly secretes, or indirectly gives rise to an inhibitor of ovex-induced regression (perhaps a non-prolactin mammogen) or some combination of hormones present in MtT-bearers inhibits ovex-induced regression.

We realize that the endocrine environment of an animal bearing a mammosomatotropic tumor is highly abnormal and very different from that of a normal animal. However, the detection and identification of an inhibitor of ovex-induced regression in MtT-bearing animals may lead to the discovery of similar factors in women with estradiol receptor positive breast tumors that fail to achieve ovariectomy-induced remission. Any explanation for failure of ovariectomy-induced remission based on clonal selection or on a genetic defect would involve loss of the mechanism for regression and would presently imply an unfavorable outlook for reversing the ovariectomy non-responsive state. Any explanation based on environmental or hormonal factors implies reversibility removal of the inhibitor should lead to remission. We think that every effort should be made to find and identify such factors and our laboratory is currently using the MTW9 tumor system for doing this.

The Effects of High Dose Progesterone on Growth of MTW9 Mammary Tumors

The early studies of Macleod and coworkers led us to an interest in the effects of progesterone on growth o MTW9 (59). Ovarian hormones had been shown to b

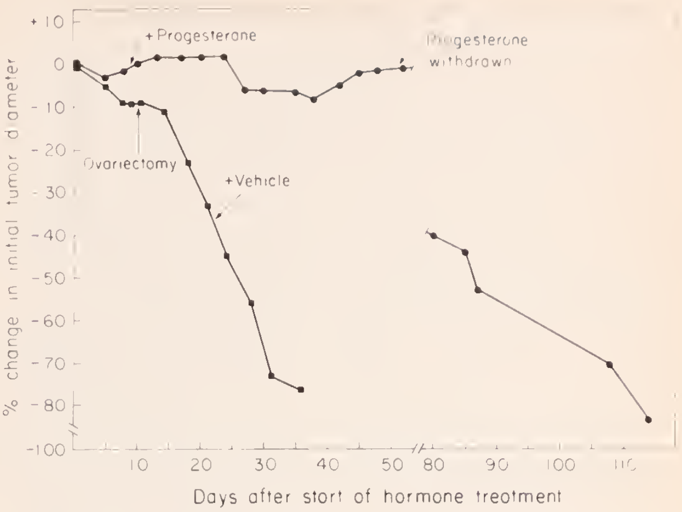

FIG. 2. *Effect of Ovariectomy on Growth of MTW9-PD in Rats Receiving Daily Injections of Progesterone (10 mg/day).* Rats bearing MTW9-PD (MTW9-PD mammary tumors were obtained by daily administration of perphenazine followed by host withdrawal from the drug when implants had attained average diameters of 1.0 to 1.5 cm.) received two daily s.c. injections of progesterone (10 mg/day, n = 5,) ●, or equal volumes of steroid suspending vehicle (n = 4) ■. After treatment for ten days, all rats were ovariectomized as indicated and progesterone administration continued. Change in average tumor diameter (3 diameters/3) is expressed as a percent of the average diameter at start of treatment (initial tumor diameter). Mammary tumors were 1.0 to 1.5 cm, average diameter before start of treatment. Points represent mean values. On day 52, progesterone-treated rats were taken off progesterone and tumor measurement continued as indicated.

required both for early tumor growth and for long term viability. When only progesterone was administered to ovariectomized rats implanted with both MtT and MTW9, the mammary tumor grew better than when only estradiol was given (Table I). However, administration of estradiol plus progesterone completely restored the growth-stimulating effect of the ovaries (59).

Ovariectomy of rats bearing MTW9-MtT or MTW9-P leads to cessation of growth and tumor regression respectively (60). These growth effects suggest loss or deprivation of some ovarian tumor growth factor (estradiol or progesterone?). Rats bearing MTW9-MtT or MTW9-P have serum progesterone concentrations which are about two to three fold higher than normal (4). This is probably due to the luteotropic effect of the elevated PRL found in these animals (37). Although serum progesterone is only moderately elevated, it may stimulate or inhibit mammary tumor growth or act synergistically with PRL to affect growth (9). For the reasons given, we investigated the role of progesterone in MTW9.

In the studies to be described, we administered pharmacologic doses of progesterone to rats bearing MTW9-MtT or MTW9-PD. Suspensions of 1, 4, 5, or 10 mg progesterone per ml were made in steroid-suspending vehicle. The total daily dose of progesterone (1, 4, 5, or 10 mg) was administered as two subcutaneous injections (at 9 a.m. and 4 p.m.) made at sites remote from the tumors. Bilateral ovariectomies were carried out under ether anesthesia.

TABLE V

*Effects of Various Endocrine Treatments on Ovariectomy-Induced Regression of MTW9-PD**

Treatment to hosts of MTW9-PD**	Ovariectomy-induced mammary tumor regression***
ACTH (2-9U/day)	yes
17-hydroxy progesterone caproate	
(4mg/day)	yes
(10mg/day)	yes
bovine growth hormone (4mg/day)	yes
implantation of MtTW5-OM****	yes
ovine prolactin	
(2mg/day)	yes
(4mg/day)	yes
bovine prolactin (12mg/day)	yes
ACTH (8U/day) + Bovine growth hormone (10mg/day) + Ovine prolactin (10mg/day)	yes
implantation of MtTW10*****	no

* MTW9-PD mammary tumors were obtained by daily administration of perphenazine followed by host withdrawal from the drug when tumors had attained average diameters of 1.0–1.5cm. Hosts of MTW9-PD manifest a normal estrus cycle, have normal serum prolactin concentrations and regress after ovex.

** Hormones were administered daily in multiple doses and for varying time periods (7–30 days) and were continued after ovex.

*** Data summarized from Diamond et al, Reference 67.

**** A growth-hormone-secreting pituitary tumor variant of MtT developed in our laboratory which secretes large amounts of growth hormone but little prolactin (75). MTW9-PD-bearing rats were ovariectomized when MtTW5-OM measured 1.5–2.0 cm average diameter.

***** MTW9-PD-bearing rats were ovariectomized when MtTW10 measured 1.5–2.0 cm average diameter.

Figure 2 shows that progesterone in high dose inhibits ovex-induced regression of MTW9-PD. Administration of 10 mg of progesterone daily to animals bearing MTW9-PD both before and after ovex results in only very slight changes in tumor size. These changes are similar to those observed for MTW9-PD in untreated control rats. Daily administration of 5 but not 1 mg progesterone also prevented ovex-induced regression. In contrast, administration of 5 μg estradiol benzoate per day to rats bearing MTW9-PD, when started at the time of ovex, did not prevent ovex-induced regression (data not shown). No dose of estradiol that we have tested prevents the regression.

Figure 2 also shows that cessation of progesterone administration leads to tumor regression similar to that observed for control rats after ovex. After progesterone withdrawal, tumors regressed to less than 80% of their initial size. In preliminary experiments, rats treated with high dose progesterone had normal serum concentrations of PRL; hence, inhibition of ovex-induced regression elicited by high dose progesterone did not appear to be due to an increase in serum PRL.

Although MTW9-MtT does not regress after removal of the ovaries, it does stop growing. It seemed logical to determine whether high dose progesterone would also prevent response to ovex in MTW9-MtT. Figure 3 shows that growth of MTW9-MtT ceases after ovex and that the administration of 5 μg estradiol benzoate per day from day of ovex failed to prevent cessation of growth. In contrast, 4 mg progesterone per day resulted in restoration of growth, suggesting that removal of progesterone may account for cessation of growth after ovex.

In spite of the large doses of progesterone required to inhibit ovex-induced regression of MTW9-PD (5 and 10 mg/day) and those used to restore growth of MTW9-MtT after ovex (4 mg/day) no effects of progesterone were observed on the growth of either tumor in intact rats. These studies differ from those of Huggins and coworkers who showed that high dose progesterone accelerated DMBA-mammary tumor growth (7, 20, 21).

In our studies, the lack of response to the steroid in intact rats may be related to the moderately elevated serum concentrations of progesterone found in the tumor-bearing rats (4). The high concentration of progesterone may be sufficient to produce the maximum physiological effect and any further hormone would then be ineffective in stimulating greater tumor growth. Ovex leads to very low concentrations of progesterone in tumor-bearing rats (unpublished observation). Our effects of progesterone on tumor growth occurred only after ovex, that is, at a time when elevated serum progesterone was decreased to very low levels; hence, the effect may be due to simple replacement of the progesterone loss. This interpretation would explain the effects of progesterone on restoration of MTW9-MtT growth after ovex as well as prevention of ovex-induced regression of MTW9-PD.

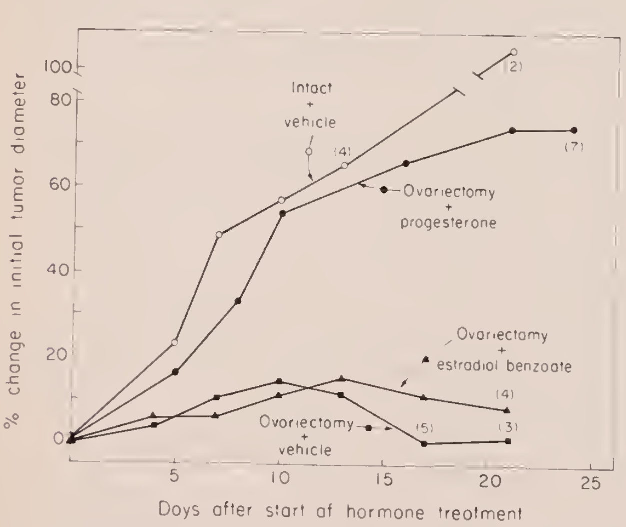

FIG. 3. *Effect of Progesterone and Estradiol Benzoate Administration on Growth of MTW9-MtT in Ovariectomized Rats.* Rats bearing MTW9-MtT were ovariectomized on day 0 and received s.c. injections of progesterone (4 mg/day in 2 daily injections, n = 7, ●) or estradiol benzoate (5 μg/day, n = 7, ▲) or equal volumes of steroid suspending vehicle (n = 6, ■). Intact tumor-bearing controls (n = 6, ○) received vehicle only. Change in average tumor diameter (3 diameters/3) is expressed as a percent of the average diameter at start of treatment (initial tumor diameter). On day 0 mammary tumors were between 1.0 and 2.0 cm average diameter. Points represent mean values. Numbers in parentheses indicate number of rats remaining in each group.

When the known endocrine abnormalities (Table III) of MtT bearing rats were simulated in rats bearing MTW9-PD, our studies failed to find a hormone that would prevent ovex-induced regression (67). PRL, growth hormone and ACTH failed to inhibit ovex-induced regression. Because PRL has been reported to stimulate adrenal progesterone in ovex rats (70), we also administered large doses of 17-hydroxyprogesterone caproate, a long-acting progestational agent, to MTW9-PD bearing rats but ovex-induced regression was not inhibited (67). In the present report, we found that progesterone did inhibit ovex-induced regression in MTW9-PD. We do not think that progesterone is the factor in MtT-bearers responsible for inhibition of ovex-induced regression, although it is the only substance that we have found so far that has this effect. Serum progesterone concentrations were essentially the same and only moderately elevated (2-3 times normal) in hosts of MTW9-MtT and MTW9-P. However, at this level of progesterone, MTW9-P regresses after ovex while MTW9-MtT does not, making it unlikely that progesterone is the inhibitor of ovex-induced regression in MtT-bearing rats. It is possible that high serum progesterone acts indirectly by stimulating pituitary secretion of a substance (not PRL, growth hormone or ACTH) that inhibits ovex-induced mammary tumor regression. Another possibility is that progesterone may inhibit regression by a direct action on tumor cells.

Inhibition of ovex-induced regression of MTW9-PD by high dose progesterone is surprising when one recalls that large doses of the long-acting progestational agent, hydroxyprogesterone caproate, was completely unable to prevent tumor regression. However, the compound has been shown to have biological effects different from those of progesterone (71). In terms of tumor growth needs, hydroxyprogesterone caproate may not be as biologically active as progesterone or it may be metabolized differently than the physiological hormone.

MTW9-MtT grows in a highly abnormal endocrine environment, whereas hosts of MTW9-PD probably have normal concentrations of most hormones (4). These differences may influence the way progesterone is metabolized. The pattern of progesterone metabolites has been shown to vary with the animal's endocrine status (72). In addition, the endocrine environment can influence the way a mammary tumor metabolizes steroids (73). Progesterone can also influence synthesis of its own receptor as well as exert an influence on its own metabolism (50–

52, 74). For these reasons, it is possible that in MTW9-PD bearing rats, progesterone may be metabolized to a product which prevents ovex-induced mammary tumor regression, whereas in the highly abnormal hormonal environment of the MtT-bearer, progesterone may be metabolized to a more growth active product. It would be of interest to compare the metabolic products of progesterone in hosts bearing MTW9-MtT, MTW9-P, MTW9-PD and in normal rats.

Conclusions

In the present report we have attempted to show that progesterone plays an important role in growth and/or regression of both rat and human breast cancers. Whether the reported actions of progesterone on mammary tumors are related to physiologically important processes or are pharmacologic effects remains to be clarified. The relationship that may exist between the role of progesterone in human breast cancer and the effects of the steroid on MTW9 is under further study.

The effects of progesterone on growth and on inhibition of ovariectomy-induced tumor regression of MTW9 mammary tumors show that MTW9 is an effective model system for studying the effects of progesterone as well as other endocrine factors which influence breast cancer growth.

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Hairy Cell Leukemia: Historical Aspects and Bone Involvement†

ROBERT L. ROSENTHAL, M.D.,* GERMAN C. STEINER, M.D.,** and BENAJMIN S. GOLUB, M.D.***

Abstract

An historical review describes the original identification and characterization of the disease, now known as hairy cell leukemia, by Nathan Rosenthal at The Mount Sinai Hospital, N.Y. The unusual finding of bone lesions in hairy cell leukemia is discussed in the presentation of a patient with bilateral infiltration of the femoral heads with excellent response to cobalt-60 irradiation.

Background

The disease now universally known as hairy cell leukemia was recognized at The Mount Sinai Hospital by Nathan Rosenthal in the early 1940's. He observed that a small number of patients, about 2% of all leukemias, with peculiar reticulum-lymphocytic-like cells in their blood and bone marrow, exhibited a relatively chronic, noninfiltrative disease. Because of the reticulum-like appearance of the characteristic cells, these patients often had been diagnosed as having very malignant diseases such as reticulum cell sarcoma or acute leukemia. Lymph nodes, spleen and liver sections were frequently diagnosed as reticulum cell sarcoma by pathologists.

Fifteen cases in a report entitled "Reticulum Cell Leukemia" were presented at the thirty-first meeting of the American Society of Clinical Pathologists in Chicago on October 16, 1952. A paper, "Reticulum Cell Leukemia: a Clinical and Hematologic Entity," by Nathan Rosenthal and Stanley L. Lee, was submitted at about the same time for publication in the American Journal of Clinical Pathology. The manuscript began:

> "During the last seven years we have encountered seventeen cases which form a clinical and cytologic entity which seems to have been unrecognized hitherto. These patients all have a progressive disease characterized by enlargement of spleen, liver and lymph nodes, this enlargement being due to a uniform cellular infiltration of all these organs as well as the bone marrow, with the specific cell type frequently recognizable in the peripheral blood. The cell type of these leukemias is remarkably uniform, and resembles closely the reticulum cell found in smears of normal bone marrow, spleen and lymph nodes. The clinical findings and course in these patients are also remarkably uniform. Although the diagnosis may be made readily when suspected, several of our cases were followed over considerable periods of time as diagnostic problems, until the nature of the syndrome had been clarified."

The paper also emphasized the difficulty of aspiration of bone marrow, the occurrence of hypersplenism, the beneficial effects of splenectomy, and the advisability of conservative therapy—with caution in the use of chemotherapy and radiation therapy. Profuse illustrations demonstrated the characteristic cell in the blood, bone marrow aspirates, and in imprints and tissue sections of spleen, lymph nodes, and liver.

Unfortunately, in a letter from the editor of the American Journal of Clinical Pathology dated March 23, 1953, the manuscript was rejected for publication with the comment that all reviewers (at least three) agreed: "The claim that the cases represent hitherto unrecognized findings is not valid. This is a commonly recognized condition for which the authors propose a new name."

In the 1940's and 1950's, reticulum cell leukemia was a well recognized syndrome among Rosenthal's colleagues and students in the hematology service at The Mount Sinai Hospital. In 1954, Rosenthal briefly mentioned the disease and included a microphotograph of the reticulum cell in a general review of lymphomas and leukemias (1). Not until 1958, however, did a comprehensive paper entitled "Leukemic Reticuloendotheliosis" by Bouroncle, Wiseman and Doan from Ohio State School of Medicine, excellently describe the disease and illustrate the hairy cell as it was named by Schreck and Donnelly in 1966 (2, 3). Two similar cases were reported

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From the Departments of Medicine*, Pathology**, and Orthopedics***, Hospital for Joint Diseases and Medical Center, New York, N.Y. 10035.

Requests for reprints should be sent to Robert L. Rosenthal, M.D. Hospital for Joint Diseases and Medical Center, 1919 Madison Avenue, New York, N.Y. 10035.

in 1956 and 1961 (4, 5). Rosenthal and Lee's original paper was expanded to include 25 cases and published in 1969 (6). More than 300 cases have now appeared in the literature from all parts of the world augmented by a few large recently reported series (7–9).

The enigma of the origin and nature of the hairy cell has stimulated wide investigation into its identity as a lymphocyte, plasmacyte, monocyte, histiocyte, endothelial cell or macrophage or a variable combination of two or more of these categories.

Prevalent opinion indicates that the hairy cell has various surface immunoglobulins, is a B cell, has poor phagocytic properties, contains tartrate-resistant acid phosphatase, and is unable to undergo blast transformation. However, cases revealing T-cell characteristics and other properties contrary to the above findings have been reported (8, 10–23). The diversity of findings suggests that hairy cell leukemia may encompass more than one entity. The question of whether the disease represents proliferation of a normally present cell or a neoplastic cell remains unanswered. In fact, the general identification of the hairy cell in some way with the lymphoreticulo-endothelial system by the earliest observers of the disease remains unshaken to this time.

Bone involvement in hairy cell leukemia is rare and had not been mentioned in any reports until the past few months. The following case presentation concerns the unusual complication of bilateral infiltration of the femoral heads with good response to cobalt-60 therapy.

Case Report

A 48-year-old white female had a history of easy bruising and excessive bleeding after dental surgery. An enlarged spleen had been noted three years previously. Five years before, a hysterectomy was performed with uneventful recovery.

Physical examination revealed a well developed woman with clear skin. The spleen was palpable 10 cm below the left costal margin. Liver and lymph nodes were not palpable. The hemogram revealed a hemoglobin (Hgb) of 10.5 gms, white blood cells at 8,400 with 90% hairy cells, confirmed by phase microscopy, and 3% lymphocytes, 7% granulocytes, and platelets of 70,000.

The patient was well until she developed discomfort and subsequent severe pain in the spleen, which increased in size to 18 cm. Figure 1 represents a summary of her course. Therapy with prednisone, 30 mg daily, produced transient shrinkage of the spleen to 11 cm with symptomatic relief. On tapering down the dose of prednisone to 15 mg daily, the patient experienced pain in the spleen which was found to be enlarged to 14 cm. Increasing prednisone to 40 mg daily did not provide any improvement. Therefore, a splenectomy was performed on February 17, 1972. The patient had an uneventful postoperative recovery. Platelets increased from 70,000 to a range of 160,000 to 420,000, and granulocytes increased from a 6-month preoperative average of 800 to a range of 2160 and 7260 over an eight-year postoperative period.

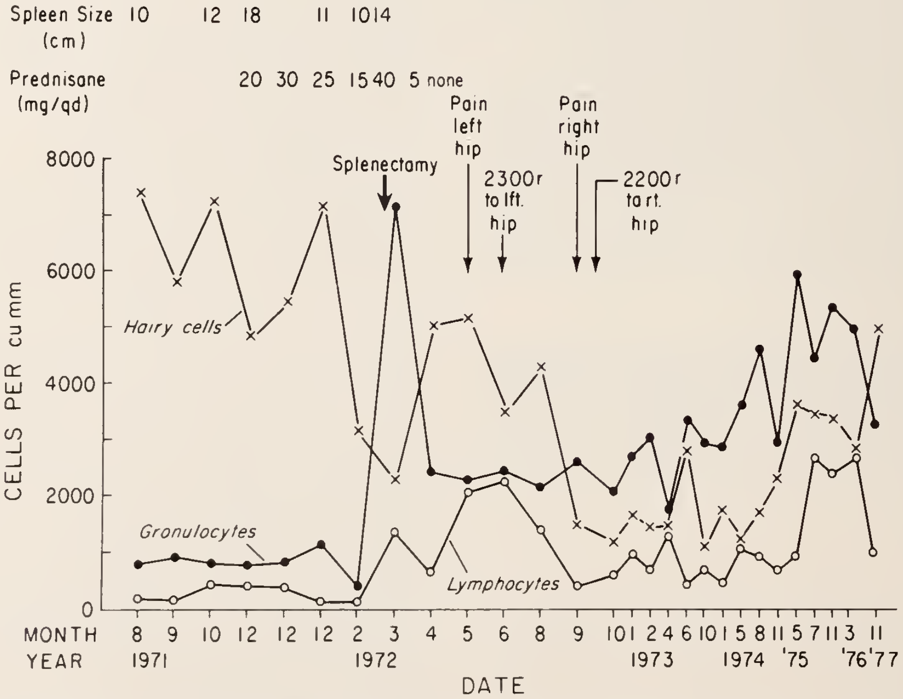

FIG. 1. Course of patient with hairy cell leukemia, showing sustained decrease in hairy cells and increase in granulocytes after splenectomy. Normal lymphocytes revealed slightly higher levels after splenectomy following originally depressed levels.

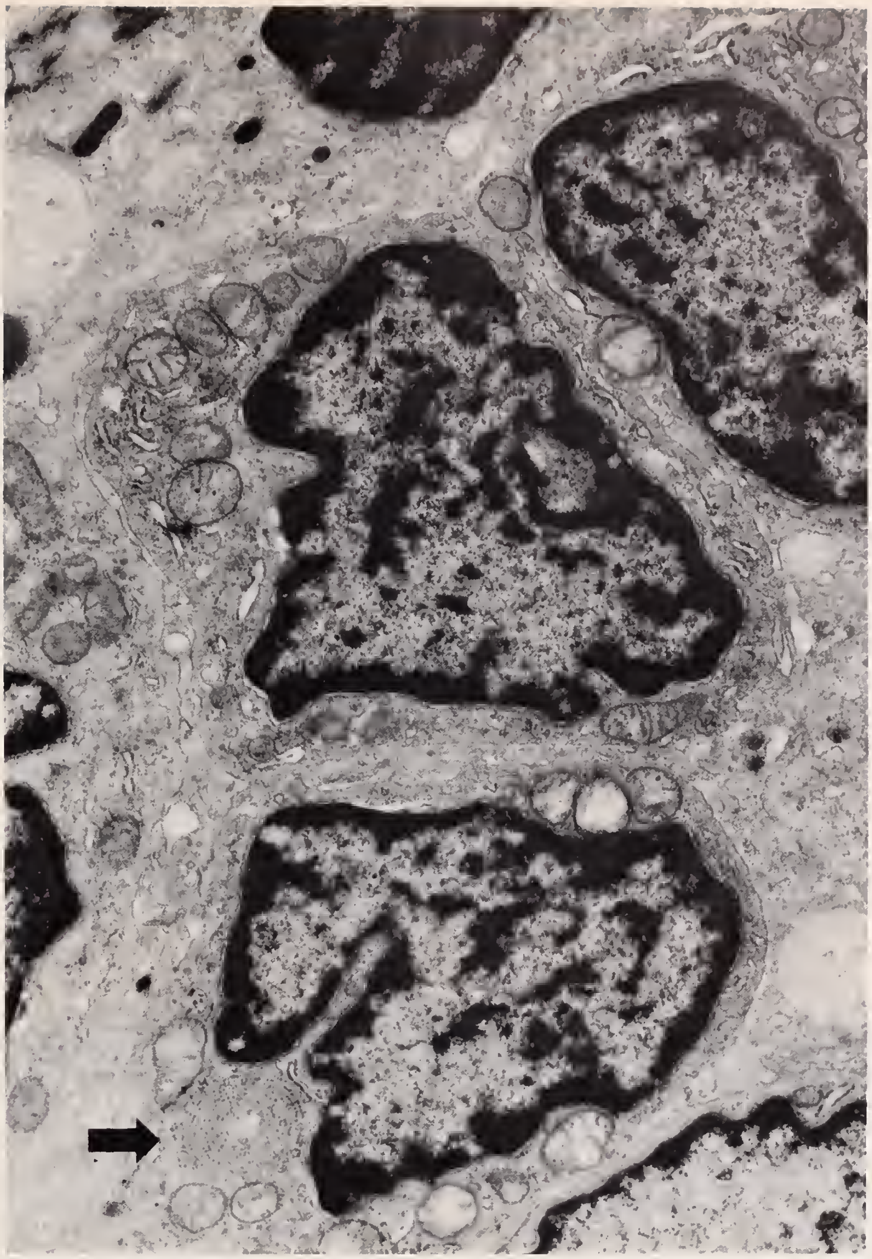

FIG. 2. Electron micrograph of a dense cellular area of the spleen. Several hairy cells are seen with indented nuclei. A ribosomal-lamellar complex is present in one cell (arrow). (× 14,200).

These changes are consistent with the recognized hypersplenism in hairy cell leukemia. It is also of interest to note that the normal-appearing blood lymphocytes increased from a range of 152 to 510 in the six-month preoperative period to 520 to 2910 following splenectomy. Almost seven years after splenectomy, the granulocytes have remained at levels of 3,000 to 6,000, while the hairy cells have remained below the above presplenectomy levels.

In October 1977, the hemoglobin was 13 gm and platelet count 340,000 per cu mm. Other studies at that time revealed: B-cells 20%, T-cells 73%, and an uptake of latex particles by only 3% of the cells. Examination of the spleen revealed a weight of 1320 gms. The cut surface was deep red throughout. Imprint and smear preparations revealed that most of the cells of the spleen were typical hairy cells. Histologically there was a diffuse infiltration of the red pulp and sinusoids by mononuclear cells. At the electron microscopic level, the hairy cells showed cytoplasmic projections in the loose areas of the tissue; these projections were less apparent in the densely packed areas (Fig. 2) (24). The hairy cell nuclei were usually indented, and the cytoplasm contained typical ribosomal-lamellar complexes (Fig. 3).

The biopsy of the liver demonstrated a sinusoidal infiltration of mononuclear cells similar to those seen in the spleen.

Ten weeks after splenectomy, the patient complained of pain in the left hip. Initially, x-rays were negative. One month later, they revealed a destructive lesion in the left femoral head and neck (Fig. 4). A biopsy revealed a uniform infiltration of mononuclear cells (Fig. 5). After 2300 rads of cobalt 60, the patient had complete relief and within six weeks could walk without pain.

Three months later, pain occurred in the right hip. Again, x-rays were negative, but because bone scan showed increased uptake, 2200 rads were given to the sacro-iliac region and the femoral head. This was followed by complete symptomatic relief and normalization of bone by x-ray examination. Patient has been asymptomatic for more than seven years.

Discussion

This case demonstrated probably the first known instance of bone infiltration in hairy cell leukemia. The

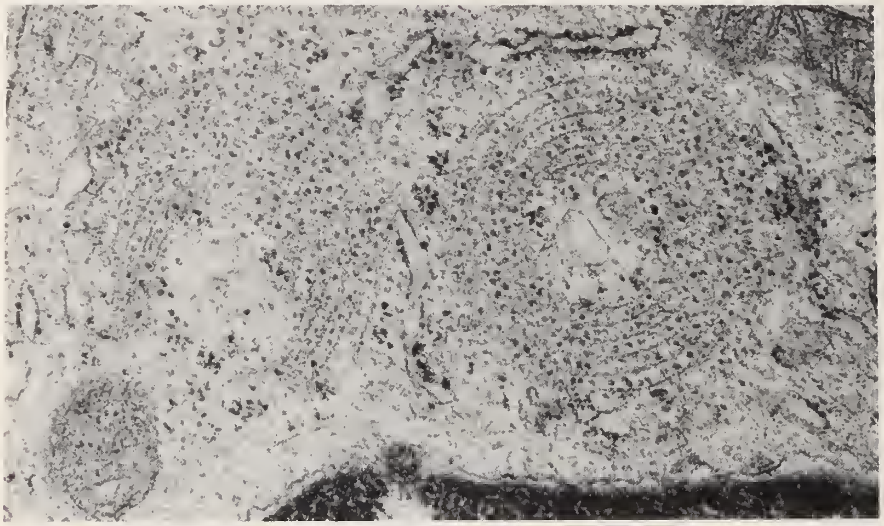

FIG. 3. High power electron micrograph showing two ribosomal-lamellar complexes. (× 38,100).

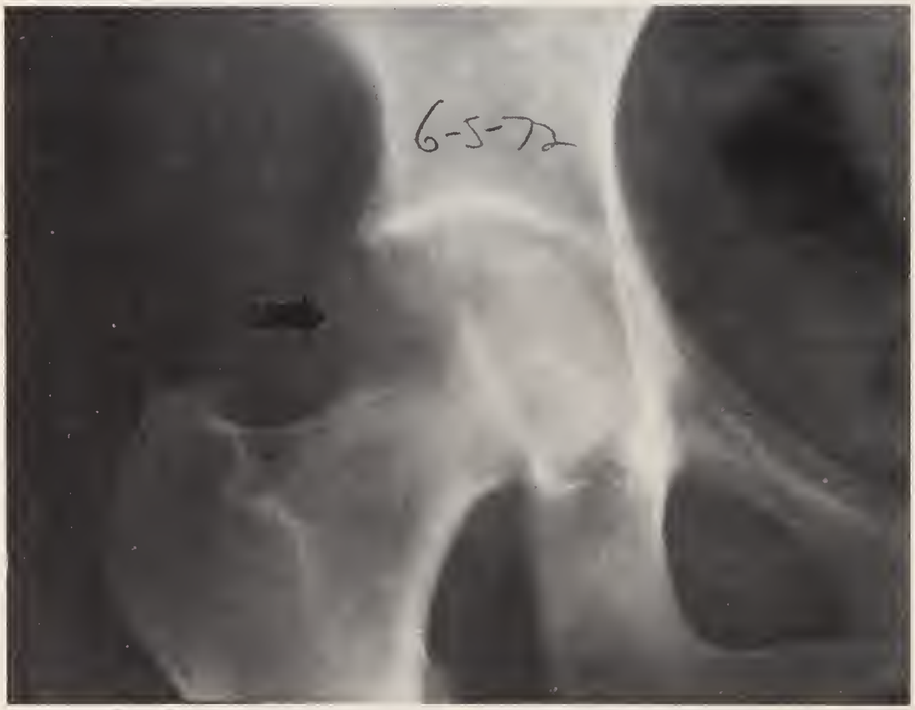

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FIG. 4. X-ray of left hip demonstrates lytic wedge-shaped bone lesion.

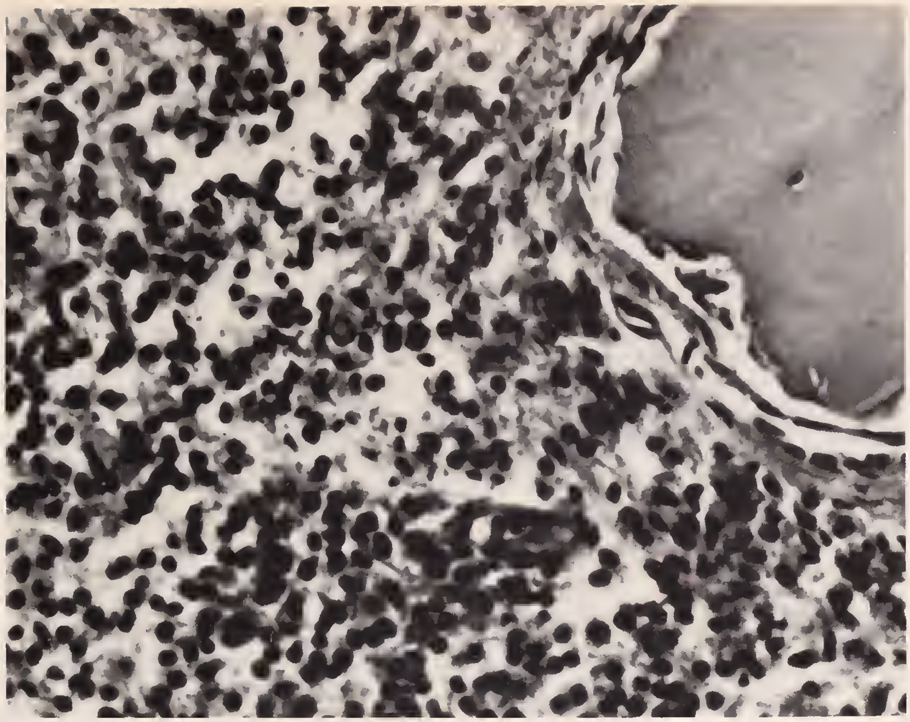

FIG. 5. Photomicrograph of biopsy from left femur. There is a leukemic infiltration of mononuclear cells of uniform size resembling the cellular infiltration of the spleen. Bone is seen at upper right corner. (× 320).

excellent response to radiation therapy was of interest because the scant information available had indicated that hairy cell leukemia generally does not respond well to x-ray therapy or to chemotherapy. An initial clinical suspicion that our patient had aseptic necrosis of the hip, possibly attributable to prednisone therapy, was definitely ruled out by the x-ray examination. It should be noted that the head and neck of the femur are unusual sites of infiltration in leukemias. Aseptic necrosis of the femoral head as far as we know, has not been reported in leukemias in general.

Subsequent to the preparation of this paper, Rhyner, Streuli and Kistler have reported three cases of lytic bone lesions in hairy cell leukemia one to three years after splenectomy (25). Two patients had lesions in the upper femur with good response to 800 and 6,000 rads of cobalt 60. The third patient showed large clear areas in x-rays of the skull with an abnormal bone scan. Biopsy revealed reticulum cells, few mature and immature plasmacytes, and numerous hairy cells. The authors conjectured that the bone lesions in hairy cell leukemia bore a similarity to those in plasmacytoma, although there is a morphological difference. It should also be noted that patients with hairy cell leukemia lack the abnormalties in immunoglobulins encountered in plasma cell diseases.

More recently, another female patient, aged 45 years, has been reported with right hip pain leading to the discovery of a lytic lesion of the femoral head (7). Similar involvement of the other hip followed, and treatment with radiation, 3,450 and 2,400 rads, produced relief of pain over five months. These findings are very similar to our experience.

At this time, the occurrence of lytic bone infiltration by hairy cell disease, that rarely shows an aggressive infiltration or tumor mass formation, must be regarded as an unusual complication to be looked for in case of any complaints of skeletal pain. In addition, bone scan can detect the lesion before it produces an abnormality on x-ray examination. This will avoid delay in treating the patient with x-ray therapy that has produced excellent results both symptomatically and objectively.

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A Review of 814 Cases of Biliary Tract Surgery from 1957–1977

CLARK HINDERLEIDER, M.D. AND LEWIS SAPERSTEIN, M.D., F.A.C.S.

Abstract

We have conducted a study of 814 cases of biliary tract surgery in an urban ghetto community hospital from 1957 to 1977, comparing our results with those of other studies reported. Our mortality of 2.2% compares favorably, encouraging us to support a more aggressive management of the acute phase of cholecystitis, especially in geriatric patients. Currently intraoperative contrast roentgenography has gained popularity in the evaluation of the biliary tree, enabling the appropriate diagnosis of symptomatic patients and ensuing operative management to be accomplished with less delay.

Calculous disease of the biliary tract has been estimated to affect one in five of the adult population of the United States. Approximately 600,000 operative procedures are performed yearly on the gallbladder and extrahepatic bile ducts and there are close to one million people each year newly diagnosed as having biliary tract disease (1). The pathophysiology and diagnosis of this entity stimulates basic scientific and clinical research resulting in constant evolution and refinement in the management of the disease (2–4). With extensive published experience giving substantiation, surgical treatment of calculous disease of the biliary system remains the definitive mode of treatment (5, 6).

The purpose of this communication is to present our experience in a teaching community hospital and to supplement our previously published experience, noting it to be consistent with the present trends in biliary tract surgery (7).

Discussion

In the Department of Surgery at the Hospital for Joint Diseases and Medical Center (HJD) in a period from 1968 to 1976 a total of 283 patients underwent surgery for biliary tract disease—219 (77.39%) females and 64 (22.61%) males. This is consistent with the statistical evidence wherein the disease state is three times more prevalent in females. In our study the racial composition of the patients was 43% Black, 29% Hispanic, and 28% Caucasian. The social histories of the patients revealed a relatively high incidence of drug (7%) and alcohol (29%) abuse. Fifty-eight percent (58%) of these were treated as private patients. This experience, added to our previous report, brings the total number of patients operated to 814, a substantial basis for examination of our treatment of biliary tract disease at this institution.

The signs and symptoms leading to diagnosis remain constant (Table I), but it appears that the patients in the current series were diagnosed earlier with less delay between diagnosis and treatment; patients were younger, the peak age being in the fourth and fifth decades compared to the sixth decade, previously, and the average duration of symptoms was 2.67 years, compared with 4.72 years, previously. This is primarily a result of diagnostic advances.

The provisional diagnosis is now confirmed with a variety of laboratory and roentgenographic procedures. Oral cholecystography remains the mainstay. Diagnostic accuracy has been reported at 97% in patients who undergo double dose studies with visualization. However, the problem of interpreting a nonvisualizing study persists. In our previous report, 95 (19%) of the patients examined had nonvisualizing studies of the gallbladder prior to operation.

All 283 patients presently reported underwent contrast roentgenography, either by oral or intravenous route. Of these, 19 (6.7%) had total nonvisualization by any method including double dose oral cholecystography. There was pathologic confirmation of a diseased gallbladder in all; however, in two patients no stones were found. The diagnosis of a calculous cholecystitis was made pathologically. It is of interest to note that both of these patients were younger males with an acute onset of symptoms (1, 5, 8–11).

From The Hospital for Joint Diseases and Medical Center, New York, N.Y. 10035.

The operative techniques have not changed substantially over this period. In the present series there was a tendency toward the use of early rather than interval cholecystectomy. Sixty-eight patients (12%) were operated on in the acute stage in the previous series compared to 47 (17%) in the present one. Of these latter 47 cases, all but seven had definitive procedures, including common duct exploration when indicated. Improvement in both operative management and preoperative care allow these to be done in the acute phase with less risk than previously reported (12–16). In the above seven cases, a cholecystostomy was done as a compromise procedure because technical considerations weighed against the safe performance of cholecystectomy, and all the patients had a limited capacity to withstand any operative intervention. These patients were all high risk because of age (over 65 years) and the severity of the disease state. Five (10.64%) of these patients died. All were over 65 years old and three had ascending cholangitis as the disease symptom complex (Table II). The mortality rate for acute phase cholecystectomy of the combined series is 7.40%. These figures are consistent with those reported in earlier studies (2, 17, 18).

The use of intraoperative diagnostic techniques to visualize and evaluate the degree and type of pathology of the entire ductal system has become more prevalent. This use of roentgenographic contrast studies has reduced the incidence of missed pathology that had previously necessitated further treatment (19). Thirty-eight percent (38%) of the patients in the present series had intraoperative cholangiography. This factor, analyzed as a single item, reduced the number of common duct explorations from 65 (12.24%) in the earlier series to the present 12 (5.19%) (P = 0.02). Moreover, all of these latter explorations were positive. The incidence of residual calculi is estimated to be 1.1% of the patients operated for calculous biliary tract disease and 4.3% of those with common duct explorations (20, 21). Since the morbidity and mortality is influenced by common duct exploration, our data stress the need for this attention to a thorough examination (22). Our mortality figures for common duct exploration for the combined series is 9.88%, but the mortality figures for the present series is 18.75%. This mortality rate represents patients over 65 years old who were acutely ill. These patients had the classic presentation of fever, right upper quadrant pain and jaundice; two had empyema of the gallbladder at the time of exploration. This figure is consistent with reports of mortality rates up to 28% in similar clinical conditions (6, 15, 21). All of these patients had a duration of symptoms of ten years or more and had periods of quiescence in their disease. The operative mortality is concentrated in this older age group, and it is not unusual for these patients to have such complications of calculous disease as acute obstructive cholecystitis and suppurative cholangitis (18, 23).

Since the natural history of biliary lithiasis is enigmatic, our data would tend to support the correction of the pathology when initially presented, providing the

TABLE I

Frequency of Signs and Symptoms Prior to Hospitalization

Signs and Symptoms	1957–1967	1968–1976
	No. of Patients (%)	No. of Patients (%)
right upper quadrant pain	531 (100.00)	283 (100.00)
nausea and vomiting	128 (24.10)	126 (44.52)
fatty dyspepsia	150 (28.20)	148 (52.30)
overweight		155 (54.77)
jaundice*	52 (9.7)	16 (5.65)

* Total serum bilirubin 1.6 mg% or greater on admission

TABLE III

Frequency of Complications

Complications	1957–1967	1968–1976
	No. of Patients (%)	No. of Patients (%)
wound infections	29 (5.46)	14 (4.95)
subhepatic abscess	3 (0.56)	1 (0.35)
subphrenic abscess	2 (0.37)	1 (0.35)
biliary fistula	2 (0.37)	1 (0.35)
pulmonary complications	25 (4.71)	9 (3.18)
phlebitis	8 (1.50)	3 (1.06)
TOTAL	69 (12.90)	31 (10.95)
over 65 years old	11 (10.00)	8 (11.94)
under 65 years old	58 (13.70)	23 (10.65)

TABLE II

Mortality Rates

Conditions	1957–1967		1968–1976	
	No. of Patients	Deaths (%)	No. of Patients	Deaths (%)
nonacute	463	8 (1.7)	236	1 (0.42)
acute	68	4 (5.8)	47	5 (10.64)
under 65 years old	423	5 (1.1)	216	1 (0.46)
over 65 years old	108	7 (6.4)	67	5 (7.46)
cholecystectomy only	455	7 (1.5)	259	2 (0.77)
common duct exploration	65	5 (7.6)	16	3 (18.75)
TOTAL	531	12 (2.25)	283	6 (2.12)

TABLE IV

Comparative Table: Morbidity and Mortality

Institution and Study Period†	No. of Patients	Morbidity %	Mortality %
University of Umea Umea, Switzerland (1962–70)	3257	Not recorded	0.9
Peninsula General Hospital Salisbury, Maryland (1946–63)	1500	7.4	1.8
Université de l'Hopital Cantonal Geneva, Switzerland (1957–66)	1103	15.8	2.9
New York Hospital Cornell Medical College (1932–74)	10,008	6.9	1.77
Virginia Mason Medical Center Seattle, Washington (1955–65)	1467	7.0	0.9
Ohio State University School of Medicine Columbus, Ohio (1951–70)	3012	16.5	1.1
Altoona General Hospital Altoona, Pennsylvania (1953–73)	2600	1.8*	2.2
St. Joseph General Hospital North Bay Civic Hospital Ontario, Canada (1966–70)	1000	12.9	1.1
Hospital for Joint Diseases and Medical Center New York, New York (1957–76)	814	12.3	2.2

* Pulmonary and urinary tract complications only

† Based on Glen, F., McSherry, C.K. Calculous biliary tract disease. Current Problems in Surgery, June 1975.

general medical conditions permit. This would avoid the increased risk encountered if operative treatment is delayed (1, 24).

Although there was no objective evidence of retained stones in the present series, five patients (1.77%) had a recurrence of symptoms which were labelled postcholecystectomy syndrome during the follow-up period of at least four years; none underwent exploration because there were not significant findings on physical or laboratory examination or on contrast roentgenography.

Our mortality (Table II) and complication (Table III) rates are consistent with the reported literature reviews (Table IV) (1, 5, 21, 23). The overall complication rate is 10.95% and the average duration of stay has fallen from 23 days to the present 15 days. It is of interest to note that the postoperative complication rate is not substantially different in the over sixty-five year old group. This would reflect a greater facility in the general medical management of the geriatric patient as well as a more acute understanding of the pathologic course of biliary tract disease in this age group.

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Acute Intestinal Obstruction

ANIL KUDCHADKAR, M.D., MULJI C. PAUWAA, M.D., F.R.C.S., AND JOSEPH R. WILDER, M.D., F.A.C.S.

Abstract

A retrospective study of 165 cases of acute intestinal obstruction treated at the Hospital for Joint Diseases and Medical Center between 1961 and 1977 is presented. One hundred and eighteen of these cases were of small bowel obstruction and 47 were of large bowel obstruction. An analysis of etiologic factors is discussed.

Problems experienced in the prompt diagnosis and treatment of these cases, especially cases of strangulation obstruction and early postoperative intestinal obstruction, have been emphasized. A study of our cases showed that approximately 35% of cases of strangulated intestinal obstruction did not manifest so-called classic symptoms of the disease.

An aggressive approach, with prompt surgical intervention as opposed to nonoperative management of obstruction with a long tube has been stressed at this institution and emphasized in this paper as being the most successful means of correcting acute intestinal obstruction.

Introduction

Intestinal obstruction is a serious disease and approximately 7,000 people die from this per year in the United States (1). It comprises approximately 20% of all acute surgical admissions (2). Intestinal obstruction, regardless of cause, is a surgical emergency and should be treated by surgical intervention.

In the early part of this century a mortality rate of 30% to 50% in cases of intestinal obstruction was not uncommon (3). However, in the past four to five decades, a significant reduction in the death rate from acute intestinal obstruction has been achieved. Success in the treatment of acute intestinal obstruction depends to a great extent upon early diagnosis, skillful management and recognition of the importance of treating the pathophysiologic effects as well as the cause of obstruction. However, if any one factor is to be stressed as being of utmost importance in the successful management of intestinal obstruction, it would be the time factor.

The aim of the present study is to review the cases of intestinal obstruction encountered at this institution during a seventeen-year period (1961-1977) and to point out the hazards of using a long tube for the treatment of intestinal obstruction.

Materials and Methods

Case records of patients admitted with intestinal obstruction to the Hospital for Joint Diseases and Medical Center during the years 1961 to 1977 were reviewed. All cases of obstruction diagnosed by history, physical examination and x-ray were included. Cases other than mechanical bowel obstruction, such as mesenteric vein thrombosis, ileus, etc., were excluded. This study, therefore, represents 165 cases of mechanical bowel obstruction occurring in 161 patients.

Age, Sex, Race

Intestinal obstruction may occur at any age, though it is rare in children and young adults (2). Its incidence rises in middle age and reaches a plateau above 50 years of age. In the present series, age ranged from nine months to 88 years, with an average age of 59.5 years.

There was no significant difference in the number of males and females who were treated at our institution for intestinal obstruction (77, 88).

The majority of the patients were Black.

Associated Medical Conditions

This institution serves a community in which the majority of adults are addicts. This factor carried through in our series, with 59.9% of the patients being addicted to alcohol and/or heroin and of poor nutritional status. The albumin level was below 3 gm% in 55% of the cases. Also, 53% of the cases had associated hypertension, diabetes, heart problems or compromised liver or kidney function. These played a significant role in the mortality.

Diagnosis

The classical symptom triad of intestinal obstruction, namely, crampy abdominal pain, vomiting, and constipation was present in 80% of the cases. Eighty-five per-

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From the Department of Surgery, Hospital for Joint Diseases and Medical Center, and Mount Sinai School of Medicine, CUNY, New York, N.Y.

cent of the patients experienced at least two components of this triad. Abdominal distension and hyperactive bowel sounds were present in 88% of the cases. Clinically, 22.5% of the cases did not show any signs of dehydration. Sixty-two percent of the cases had signs of mild dehydration, 11.5% had moderate dehydration, and 4% had severe dehydration. Laboratory studies of hemoglobin, hematocrit, BUN and urinary specific gravity corroborated the clinical assessment of the state of dehydration. Twenty-five percent of the patients showed electrolyte abnormality, mainly hypokalemia.

Obstructive series x-ray studies were performed routinely in all cases and confirmed the diagnosis in 86% of the cases. The diagnosis was equivocal in 9% of the cases and nonconfirmatory in 5% of the cases. Special contrast studies were done whenever the diagnosis of obstruction was uncertain. Iodinated aqueous media, such as gastrograffin, were in use on the patients in the earlier part of the series. More recently we have used thin barium sulphate suspension with more satisfactory diagnostic results. Barium enemas were given in cases where obstructive lesion of the colon was suspected.

Causes of Obstruction

One hundred eighteen cases (71%) of intestinal obstruction occurred in the small bowel and 47 (29%) in the large bowel. The most common causes of obstruction encountered were postoperative adhesion, carcinoma and hernia. Other less common causes are shown in Table I.

TABLE I

Causes of Obstruction

Cause	No. of Cases	% of Total
*adhesions (postoperative)	75	46
hernia	33	20.0
malignancy	32	19.9
*volvulus	16	9.6
diverticulitis	4	2.4
intussusception	4	2.4
miscellaneous	8	4.8

* Seven cases had volvulus secondary to adhesions.

TABLE II

Postoperative Adhesions

Initial Surgery	No. of Cases
Infracolic (84%)	
appendectomy	18
hysterectomy	17
colorectal	14
laparotomy	9
noble plication	3
m. diverticulectomy	1
aortofemoral bypass	1
Supracolic (16%)	
gastric	5
gallbladder	5
splenectomy	2
Total:	75

TABLE III

Malignancy in Bowel Obstruction

Mechanism of Obstruction			
A. Obstruction due to tumor mass			19
sigmoid adenocarcinoma	8		
splenic flexure adenoca.	2	Large bowel obstruction	
trans. colon adenoca.	3		
Cecal adenoca.	2		
appendiceal carcinoma	1		
ileal lymphoma	2		
ileal adenocarcinoma	1		
B. Obstruction due to diffuse metastatic carcinomatosis			8
pancreatic carcinoma	2	Small bowel obstruction	
ovarian carcinoma	3		
stomach carcinoma	3		
C. Obstruction due to local infiltration by tumor			5
sigmoid carcinoma	3		
urinary bladder carcinoma	1		
hodgkin's disease (retroperitoneal)	1		
Total:			32

TABLE IV

Hernias Causing Bowel Obstruction

Type of Hernia	No. of Cases	
External		28 (85%)
femoral	10	
inguinal	9	
umbilical	5	
incisional	4	
Internal		5 (15%)
paraduodenal	2	
around ileostomy	1	
around colostomy	1	
hole in mesocolon	1	
Total		33 (100%)

Adhesions

Of the 75 cases of intestinal obstruction due to postoperative adhesions, the majority (80%) were of the small bowel. In seven cases, adhesion led to volvulus, three of the small bowel, two of the cecum and two of the transverse colon. It is interesting to note that in 65% of the cases the initial surgery had been pelvic (appendectomy, hysterectomy and colorectal) (Table II).

Malignancy

There were 32 cases (20%) of intestinal obstruction caused by malignancy. Fifteen of these cases were due to primary adenocarcinoma of the large bowel and the remaining 17 cases were of the small bowel, with the

TABLE V

Miscellaneous Causes of Obstruction

Cause	Site	Mechanism	No. of Cases
superior mesentery artery compression	duodenum	compression	1
pancreatitis	jejunum	fat necrosis	1
Crohn's disease	ileum	twist stricture	1
Meckel's diverticulum	ileum	post infl. adhesion	1
mes. fibromatosis	ileum	kink & compression	1
inflammatory mass. (nondiverticular)	sigmoid	stricture	1
fecal impaction	rectum	obturation	2
		Total:	8 (4.8%)

majority of the tumors involved being metastatic. The mechanisms of obstruction are shown in Table III.

Hernia

Of the 33 cases (20%) of obstruction caused by hernias, eighty-five percent of the hernias were external and fifteen percent internal. In all cases of femoral hernia and five of the cases of inguinal hernia, the internal ring was the strangulating factor. In the remaining cases, adhesions between bowel loops and between the loops and the hernial sac were the obstructing factors. All underwent reduction of the hernia and eight (24%) of the cases required resection due to gangrene (Table IV).

Volvulus

Of the sixteen cases of volvulus, 13 involved the large bowel. Though none were gangrenous, primary resection and anastomosis were done in six sigmoid volvulus cases. As mentioned above, seven cases of volvulus were secondary to postoperative adhesions.

Diverticulitis

Four patients developed small bowel obstruction due to diverticulitis of the colon. In two cases, the small bowel was involved in the pericolic abscess wall, causing obstruction, while in the other two cases the small bowel had kinked because of adhesions between the inflamed colonic diverticuli and the small intestine. All underwent surgery and enterolysis.

Intussusception

Of the four cases of intussusception, only one occurred in an infant. This was of the ileocolic type and was reduced intraoperatively. The remaining three occurred in adults–two of the ileoileal type and one of the jejunoileal type. Resection was done in all three cases. The lead points varied, being lymphoma, lipoma and chronic nonspecific ulcer in the three respective cases.

Miscellaneous

Eight cases (4.8%) of intestinal obstruction occurred because of a variety of unusual causes as listed in Table V.

TABLE VI

"Classical" Clinical Features of Gangrene

Clinical Feature	No. of Cases Absent	% of Cases Absent
tachycardia over 100/min	4	21
severe constant pain	7	37
leukocytosis over 15,000	7	37
fever over 100° F.	7	37
*tenderness (rebound)	4	36

* Excludes strangulated hernias.

TABLE VII

Analysis of Long Tube Treatment

A.	apparently asymptomatic	5
B.	no follow-up available	4
*C.	readmitted and operated	4
	case No. 12 - gangrene & death	
	case No. 69 - intussusception - missed lipoma	
	case No. 7 & 138 - enterolysis	
D.	aspiration pneumonia & death	1
	Total:	14

* Does not include Case No. 42, that underwent enterolysis but was treated elsewhere with a long tube two weeks prior to admission.

Early Postoperative Obstruction

Sixteen patients developed intestinal obstruction in the immediate postoperative period. In nine of these cases, initial surgery was colorectal.

Differentiating early postoperative obstruction from ileus may be a difficult challenge. The clinical picture is often confused by postoperative nagogastric aspiration, postoperative "wound pain" and postoperative "wind pain." In our series, diagnosis was usually suspected on the fifth to seventh postoperative day. We found abdominal distension to be the most common feature present, encountered in 80% of the cases. Sixty-five percent of the cases had constipation and 50% had hyperactive bowel sounds. More importantly, however, is the fact that six cases (35%) had diarrhea and eight cases (50%) had hypoactive bowel sounds. Only ten of these cases were correctly diagnosed and promptly treated. Two were treated conservatively with long tube intubation and eight were reoperated after having failed to show prompt improvement.

TABLE VIII

Treatment of Intestinal Obstruction

194 Procedure	No. of Small Bowel Obstructions	No. of Large Bowel Obstructions		Total
SURGICAL				149
enterolysis	43	11	54	
resections	16	8	24	
colostomy		15	15	
reductions (volvulus & hernia)	27	10	37	
Bypass	18	1	19	
CONSERVATIVE				16
long tube	14		14	
disimpaction		2	2	
Total:	118	47	165	

TABLE IX

Complications of Obstruction

Complication	No. of Cases		Percent
* chest		34	20.6
pneumonia	22		13.3
atelectasis	7		4.2
embolism	5		3.1
* wound		40	24.2
significant infection	40		24.2
burst abdomen	2		1.2
shock (water & electrolyte depletion)		4	2.4
deep vein thrombosis		3	2.0
liver failure		4	2.4
renal failure		3	2.0
heart failure		3	2.0
pulmonary insufficiency		1	0.6
fecal fistula		1	0.6
peritonitis		2	1.2
diabetic acidosis		1	0.6
Total number of cases:		65	39.3

* Some cases had both chest and wound complications.

TABLE X

Mortality in Obstruction

Cause of Death	No. of Cases		% of Mortality
associated medical problems	10		6%
heart failure	2		
liver failure	2		
renal failure	2		
pulmonary embolism	2		
aspiration pneumonia	1		
diabetic acidosis	1		
carcinomatosis		6	4%
shock (fluid electrolyte)		2	1.0%
peritonitis		1	0.55%
Total:		19	11.55%

Of the six cases that were misdiagnosed, special contrast studies were done using thin barium sulphate solution. Surgery was delayed on an average of 75 hours. One patient died; a delay of surgery for over six days may have contributed to this mortality.

Strangulation Obstruction

The classic symptomatic features of strangulation and gangrene are absent in a substantial number of cases, making early diagnosis very difficult. In the present study there were nineteen cases (11.5%) of gangrene requiring resection. We found a tachycardia of over 100/min to be the most constant feature present, occurring in 15 of the cases. So-called classical features of gangrene were absent in a substantial number of cases, as shown in Table VI.

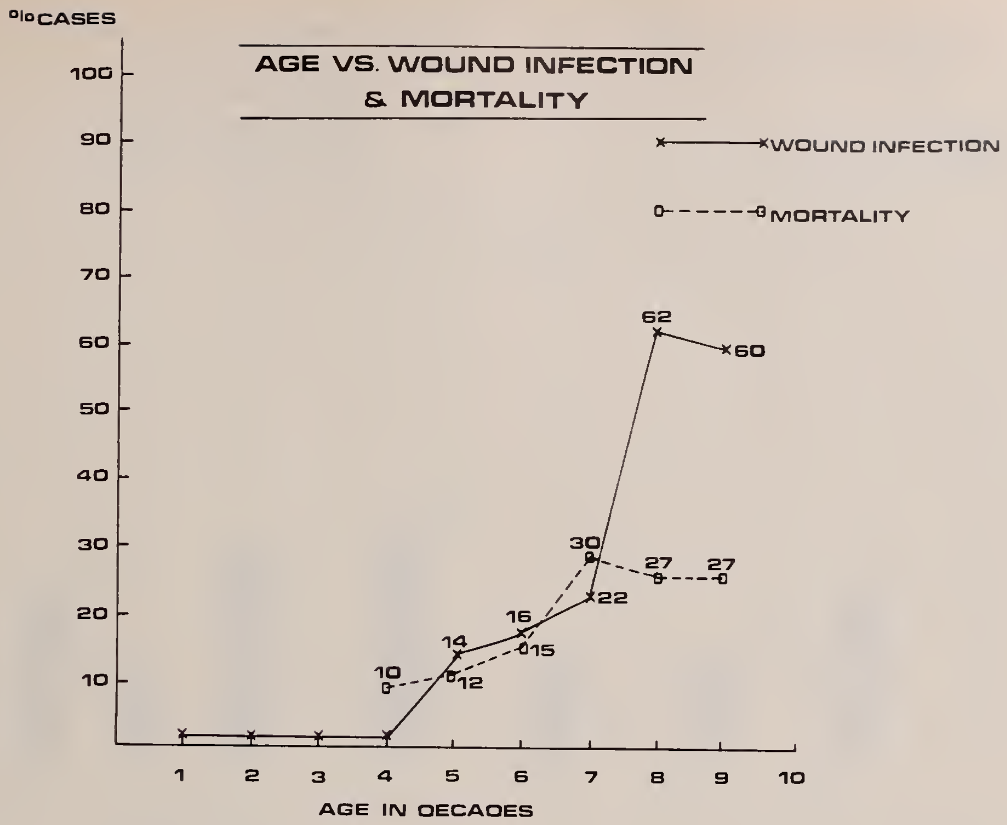
Eight patients had strangulated external hernias. All of these cases were diagnosed and treated promptly, within four hours of admission to the hospital. Of the remaining eleven cases, only eight were correctly diagnosed preoperatively. Of the three cases undiagnosed initially, two were speculated to have acute appendicitis and one to have acute pancreatitis. Two of these patients died, one from renal failure and the other from diabetic ketoacidosis.

Management

Once diagnosis of acute small bowel obstruction is made, we believe in prompt surgical relief of the cause of obstruction. The patient is prepared for surgery by the insertion of a nasogastric tube, administration of appropriate intravenous fluids and monitoring of pulse rate, central venous pressure and urinary output. On the average, six to twelve hours were spent in preparing the patients for surgery.

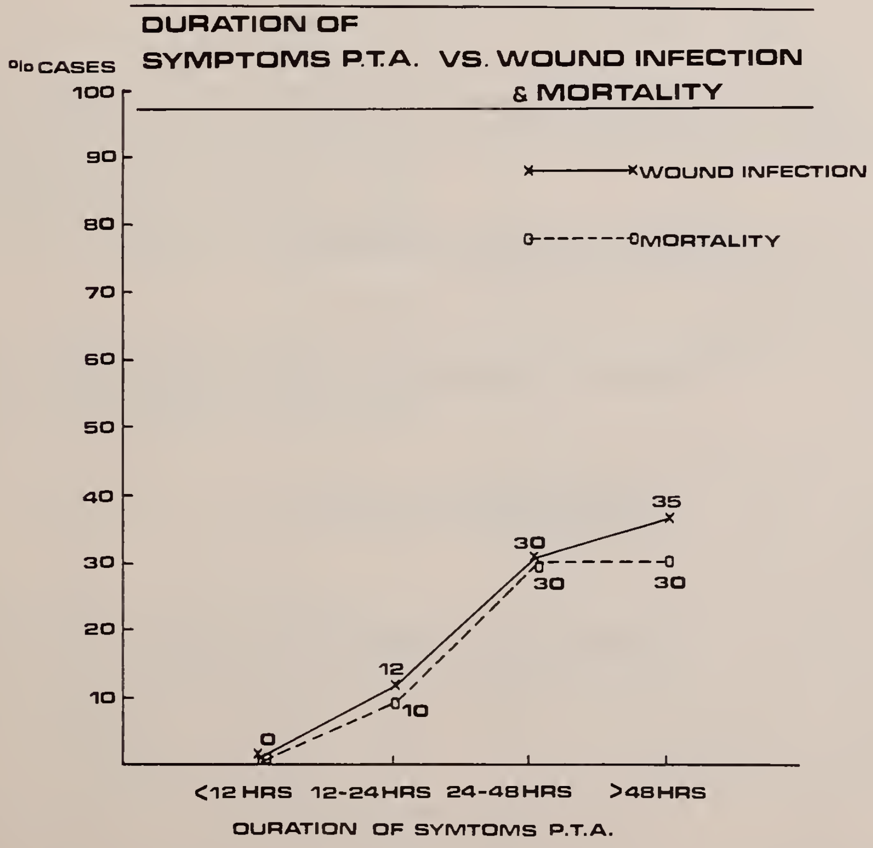
Although a large number of surgeons continue to use intubation with a long tube as a definitive treatment for intestinal obstruction, a careful analysis of fourteen such cases in our series showed some disastrous results (Table VII).

One of our cases, a 51-year-old male, was treated with a long tube only to be readmitted three weeks later with gangrene of the small bowel secondary to adhesions and obstruction. The patient died postoperatively after resection. Another case returned two weeks after successful long tube treatment. Upon readmission he was operated on and an intussusception with the lead point of a submucous lipoma was found. A third case returned one week after discharge and underwent enterolysis for adhesions; a fourth returned two weeks after discharge and



% CASES
AGE VS. WOUND INFECTION & MORTALITY
WOUND INFECTION
MORTALITY
100
90
80
70
60
50
40
30
20
10
62
60
30
27
27
22
16
15
14
12
10
1
2
3
4
5
6
7
8
9
10
AGE IN DECADES

FIG. 1.



DURATION OF SYMPTOMS P.T.A. VS. WOUND INFECTION & MORTALITY
% CASES
WOUND INFECTION
MORTALITY
100
90
80
70
60
50
40
30
20
10
35
30
30
30
12
10
0
<12 HRS
12-24 HRS
24-48 HRS
>48 HRS
DURATION OF SYMTOMS P.T.A.

FIG. 2.

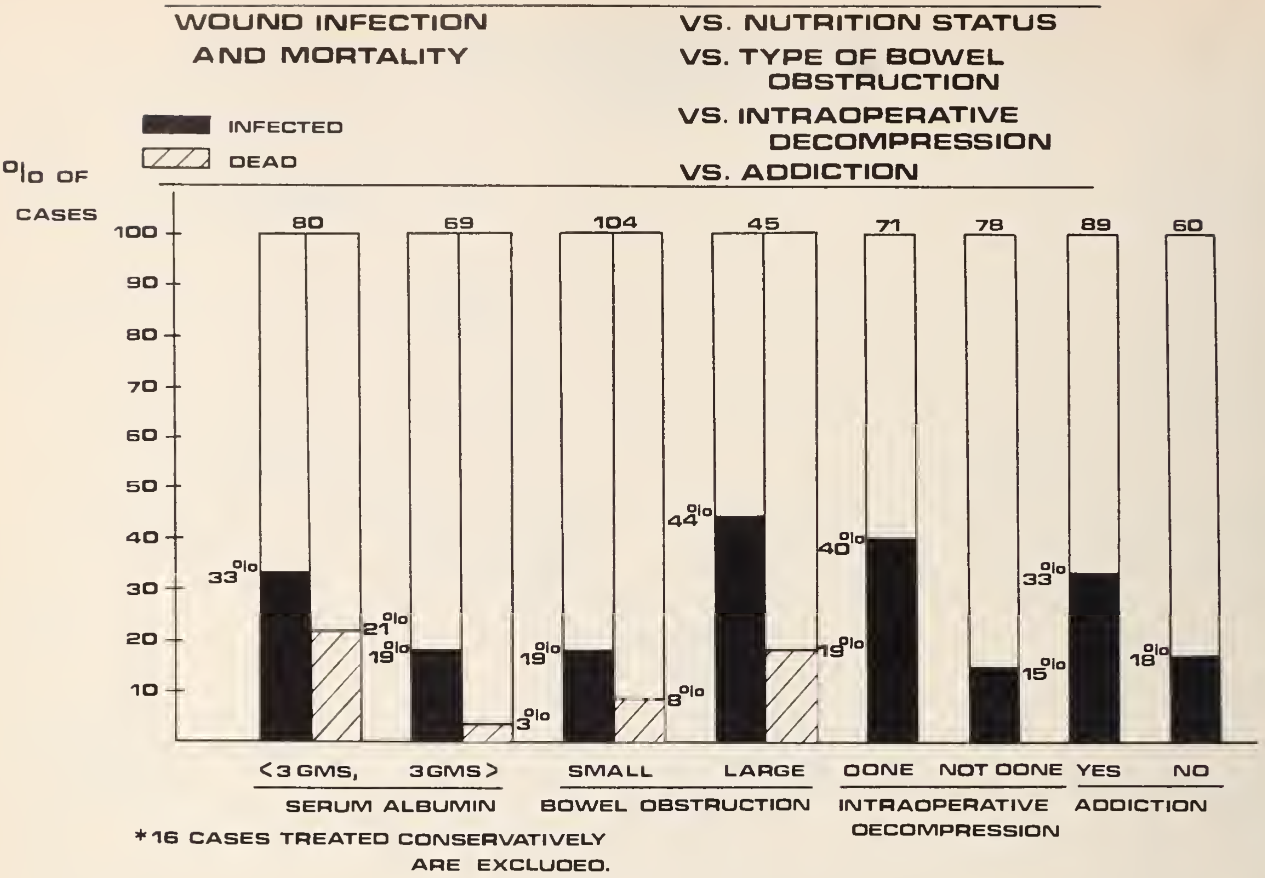


Fig. 3.

underwent enterolysis. A fifth case was treated elsewhere two weeks prior to admission to our institution with a long tube. This patient also had adhesions and underwent enterolysis.

Surgery was undertaken in 149 cases (90%). The procedures performed are shown in Table VIII. Intraoperative decompression was performed in 71 (47.6%) of the cases to relieve excessive bowel distension in order to permit safe closure of the abdomen.

Morbidity and Mortality

Sixty-five patients (39%) developed problems, with chest complication in 20% of the cases and significant wound infection in 24%. Other complications such as water electrolyte depletion, deep vein thrombosis, etc., occurred in isolated instances as shown in Table IX.

Nineteen patients (11.5%) died within a week of the initial appearance of symptoms of intestinal obstruction. Fifty percent of these had associated medical conditions that contributed to the mortality; thirty-five percent had associated carcinomatosis. Of the remaining 15%, two died of shock (fluid electrolyte depletion) and one of peritonitis (Table X).

A further analysis of mortality revealed that a significant number (64%) of those that died were above sixty-five years of age and a substantial number (60%) were operated on more than 18 hours after admission for intestinal obstruction. In addition, sixteen (84%) of these patients had a serum albumin below 3 gm%. The adverse effects of these factors–age, delay in treatment and poor nutritional status–are shown in Figures 1, 2 and 3.

Hospital Stay

The average hospital stay of our patients was 21.2 days, ranging from 10 to 108 days. This is comparable to other reports, with an average stay of 21.1 days reported by Bollinger et al and 20.8 days by Suffian et al (4, 5).

Conclusions

The etiologic factors of acute intestinal obstruction have changed quite remarkably in the past three decades. In the 1960's, strangulated external hernia was the most common cause of obstruction (6–8). At present, postoperative adhesions are recognized nationally as the leading cause, as supported by our series.

There has been a definite increase in the incidence of carcinomatous intestinal obstruction. Unfortunately, these two diseases combined offer a very poor prognosis. Six out of 32 of our patients (22%) with this combination died. An increase in the incidence of carcinoma itself may account for the increase in the carcinomatous intestinal obstruction (5). Conversely, early surgical repair of external hernias may account for the decline in the incidence of strangulated external hernias.

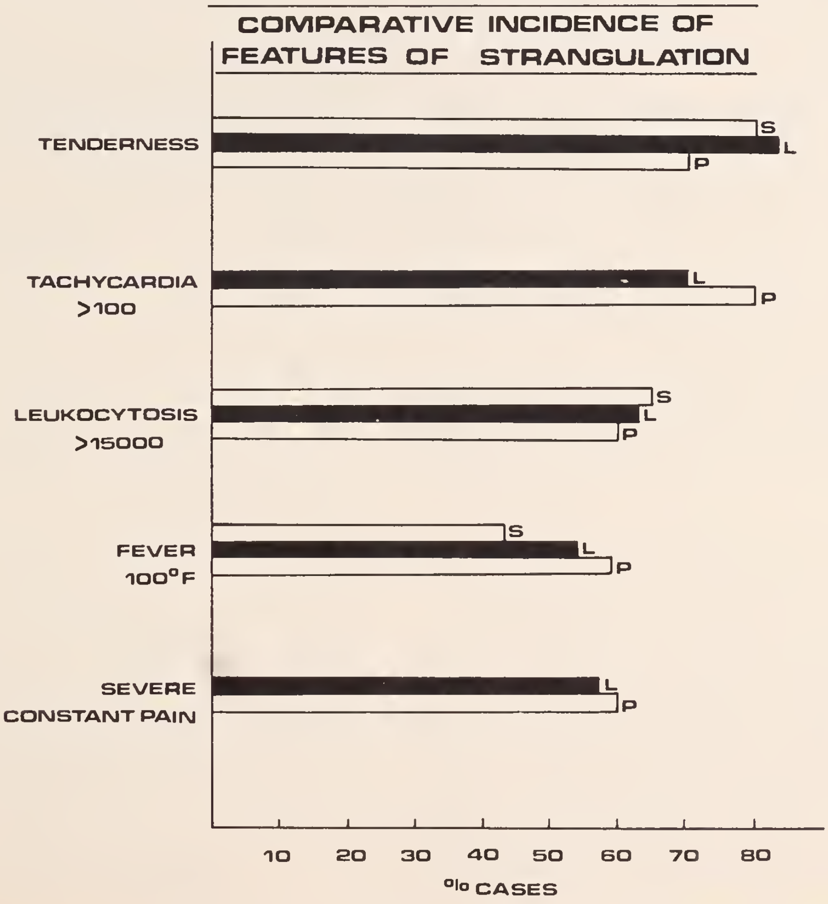
Approximately half of our cases of early postoperative intestinal obstruction occurred following colorectal surgery. Similar observations have been made by Sykes et al and Colleti et al (9, 10). In some instances, we experienced difficulty in differentiating between intestinal obstruction and ileus, a difficulty experienced by others in the field (9–11). In spite of a special interest in and an awareness of the disease at our institution, diagnosis was delayed by four to five days in six of our cases (37%).

Too often surgeons merely treat these cases with long tubes. We, however, support an early, more aggressive treatment with reexploration where indicated. Postoperative abdominal distension occurring for the first time four to five days after initial surgery is treated here as mechanical intestinal obstruction until proven otherwise. We believe that the benefits of this approach are reflected in our low mortality rate of 6.25% as compared to other reported rates of 21.4%, 22% and 15% by Miller and Winfield, Colleti and Bossart and Sykes and Schofield, respectively (9–11).

The prompt diagnosis of strangulation in cases of intestinal obstruction remains elusive (12–14). This, we believe, is frequently because of the absence of some of the classical features of strangulation, as was true in 20% of our cases (Fig. 4). Despite this, our mortality of 10.5% in cases of strangulation obstruction compares quite favorably with other reports of 28%, 32% and 30% by Silen et al, Snyder and McCranie, and Leffal and LaSalle, respectively (12–14). Once again, we believe that this is because of our aggressive approach of early surgical intervention in cases of intestinal obstruction.

We believe that the reason for the high mortality rate in cases of intestinal obstruction, particularly when compared to some of the other acute abdominal emergencies is due to the unfortunate delay in operative intervention. All too frequently the use of a long tube masks the need for, and otherwise delays, surgical intervention. In 25% of the fourteen cases in our series in which a long tube was used, we found irreversible pathology in the form of strangulation, a submucous lipoma causing intussusception and, in two cases, complete intestinal obstruction due to adhesions. A fifth patient died of aspiration pneumonia. In summary, five patients of the fourteen in whom long tubes were used encountered serious difficulties, including two deaths. In four of the patients surgery was delayed an average of ten days (Table VII).

An analysis of our morbidity rates revealed a high incidence (24%) of wound infection, that may be attrib-



S- SILEN EL AL[17] (1962) ; L- LASALLE ET AL[11] (1970); P- PRESENT SERIES

FIG. 4.

TABLE XI

Overall Mortality in Literature

Author	No. of Cases	% of Deaths
Perry et al (19)	1252	12.5
Savage et al (20)	179	12.0
Waldron & Hampton (21)	493	14.0
Lo et al (22)	150	24.0
Sufian & Matsumoto (4)	171	18.5
Present Series	165	11.55

uted to the 40% incidence of intraoperative decompression. Similar observations were made by Larsen and Pories (Fig. 1–3) (15).

Although our mortality rate of 11.5% compares favorably with other reported series (Table XI), the fact remains that five of our patients that died were observed for more than 18 hours. We believe that our low mortality rate in a group of patients with an average age of 60 years, 60% of whom were addicts and 55% of whom had serum albumin less than 3 gm%, lends considerable support to our policy of early surgical intervention whenever possible in the management of acute intestinal obstruction.

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Fibrosarcoma: The Biomathematical Approach to Late Metastases: A Case Report

ALEXANDER W. PEARLMAN, M.D.

Abstract

Distant metastases occurring many years after successful ablation of a primary tumor can be correlated with the growth dynamics of the tumor. Exponential growth is a characteristic of many malignant tumors, at least while they remain relatively small, up to a diameter of 2.0 to 2.5 cm. When a growth curve has been constructed by plotting serial measurements of tumor size, backward extrapolation of the curve will indicate the time of inception of the tumor. The period from inception to diagnosis defines the clinically silent period when occult metastases may occur. Tumor doubling times (Td) of 70 pulmonary metastases in 25 patients with soft tissue fibrosarcoma were plotted on log-probability paper. The distribution was log normal. A log-normal frequency distribution of randomly observed tumor diameters supports the concept that growth is by geometric progression (4). The survival of 25 patients, all of whom died of their disease, is recorded in months and multiples of Tds. Survival depends chiefly on growth rate. The use of Td as a yardstick of survival of the effectiveness of a particular treatment is a more realistic measure than units of time.

Introduction

Distant metastases, appearing many years after a malignant tumor has been successfully ablated, can be correlated with the growth dynamics of the tumor. This has implications for both treatment and prognosis.

While the virulence of a malignant tumor may be deduced from its size, invasiveness, duration, and histologic differentiation, these parameters are imprecise. Collins et al, in 1956, introduced the concept of tumor volume doubling time—that interval during which there is a twofold increase in volume, as a quantitative measure of growth rate (1). This biomathematical approach which gives a numerical value to tumor growth rate is based on the concept that tumor growth in human beings is essentially exponential, at least for a considerable portion of its life cycle, and remains the simplest hypothesis as to the duration of cancer (1–3). A number of tumors do grow in a Gompertzian fashion (4, 5).

Based on the assumption of a constant growth rate, a sequence of events unfolds. It requires approximately 30 tumor volume doublings for a single cell to attain a diameter of 1 cm, generally considered the smallest diagnosable size. This long silent preclinical interval may comprise as much as three quarters of the life cycle of the tumor and it is during this interval that occult metastases may occur. Should tumor growth continue at the same rate, unhindered by treatment, it would require relatively few additional doublings before tumor size would be incompatible with the life of the host (4).

When the growth curve of a tumor has been established by multiple observations of tumor size, backward extrapolation will indicate the approximate time of inception. If exponential growth is not necessarily present during the entire life of a tumor, it is reasonably well established that for moderate-sized tumors (up to 2.0 to 2.5 cm diameter) constant growth rates prevail (7, 8). The biomathematical view of exponential tumor growth clarifies many aspects of the behavior of human neoplasms and focuses on the relatively long interval between the inception of a tumor and its earliest clinical manifestations.

Case Report

The following case report illustrates that the interval between onset and diagnosis of metastatic disease can be correlated with the growth rate of the metastases which may be present as clinically undetectable microscopic foci for relatively long periods of time.

B.K., a female, aged 54 years, first noticed a 3 cm, fixed, soft tissue mass on the dorsum of her left foot in February 1959, following a minor trauma three weeks before admission. Biopsy of the mass was reported to be

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From the Department of Radiation Therapy, Hospital for Joint Diseases and Medical Center, New York, N. Y. 10035.

an undifferentiated soft tissue fibrosarcoma, and was soon followed by a below knee amputation. Radiographs of the chest, four months after surgery in August 1959 were normal. For the next eleven years she was asymptomatic and did not return for examination until wheezing respiration and cough caused her to again seek medical attention. Chest radiographs in August 1970 now demonstrated multiple pulmonary metastases, the largest in the right upper lung measuring 9.2 cm in diameter, the smallest measuring 2.0 cm (Fig. 1).

Thoracotomy and biopsy of a pulmonary nodule confirmed the diagnosis of a metastatic, poorly differentiated fibrosarcoma similar to the original tumor. The growth rates of individual pulmonary metastases were calculated by measurement of their diameters on successive serial teleroentgenograms (Table I and Fig. 2). The largest tumor in the right upper lung was irradiated with CO60, parallel opposing portals, to a central tumor dose of 2800 rads in 18 days. Tumor shrinkage was slow and incomplete, followed by regrowth.

Thereafter, and until her sudden death two years later, there was no specific antitumor therapy. Death was due to acute respiratory failure secondary to metastatic fibrosarcoma of both lungs. At autopsy, there were metastatic fibrosarcoma masses confined to both lungs and no tumor elsewhere.

Biomathematics

Tumor doubling time (Td) was calculated according to a formula proposed by Gerstenberg (quoted by Philippe and LeGal) which assumes that malignant cells divide at approximately equal intervals (9).

$$\mathrm{Td} = \frac{0.1\,(t - to)}{\log dt - \log do} \qquad (1)$$

Where *do* and *dt* are successive tumor diameters observed at an interval of *t* days. To calculate the Td, only the first and last measured diameters were considered providing that the intermediate volume measurements approximated a straight line on a semilog graph. There were eight pulmonary nodules suitable for mensuration. These are listed in Table I and their growth curves plotted in Figure 1. Nodules one to four, inclusive, were observed on six successive roentgenograms over a period of 153 days prior to irradiation of nodule one. Nodules five to eight inclusive, first appear some time after the irradiation treatment of nodule one, and their diameters

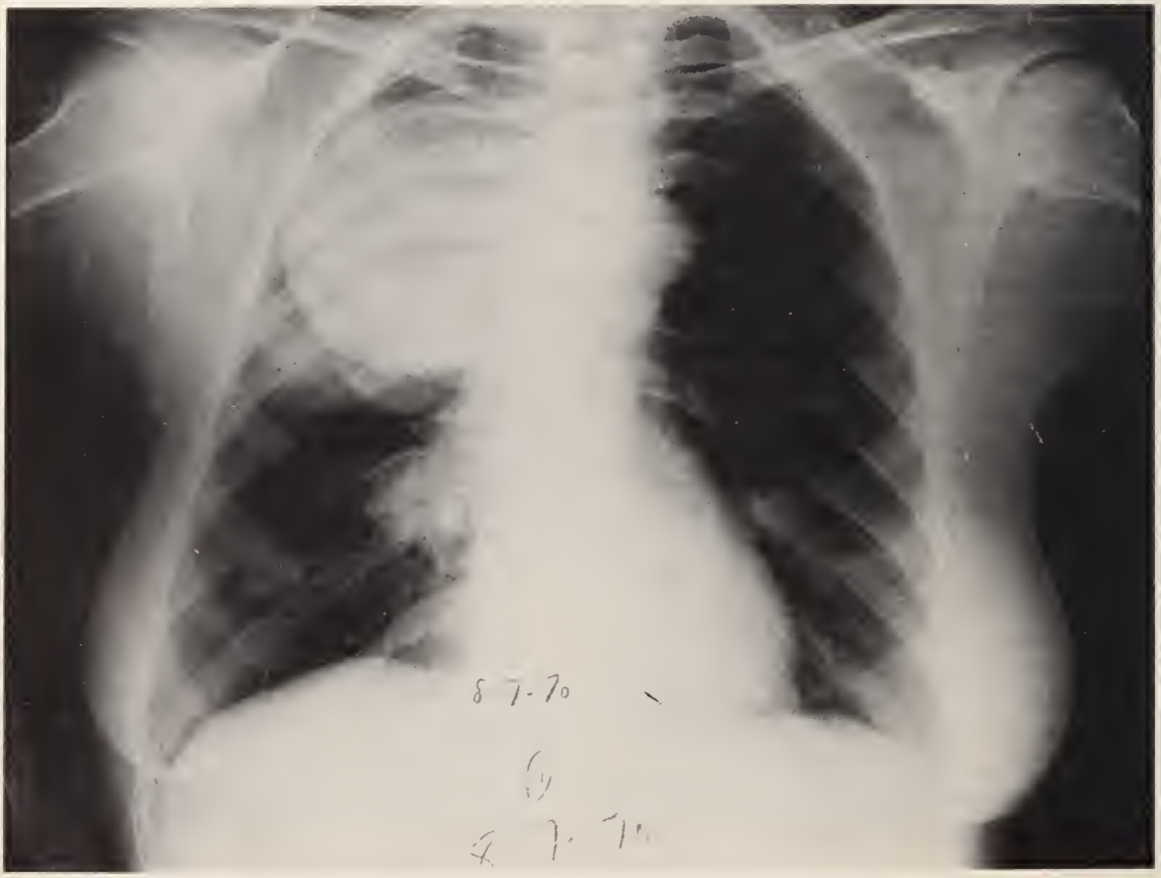

FIG. 1. Chest radiograph, February 1959, at first discovery of pulmonary metastases. The large nodule in the right upper lung was irradiated to a tumor dose of 2800 rads in 18 days with CO60 from parallel opposing portals. This was the only pulmonary irradiation this patient received.

TABLE I

Doubling Time (Td) of Pulmonary Nodules (B.K.)

No	Initial size (cm)	Final size (cm)	Period observ. (days)	Td (days)
Before Irradiation				
1	9.2	10.7	153	218
2	2.0	2.6	153	139
3	3.1	4.1	153	126
4	2.2	2.8	153	145
After Irradiation				
5	1.3	2.8	469	142
6	1.0	1.6	180	72
7	1.9	4.1	422	127
8	1.0	2.2	422	124
1a	5.5	6.5	180	257

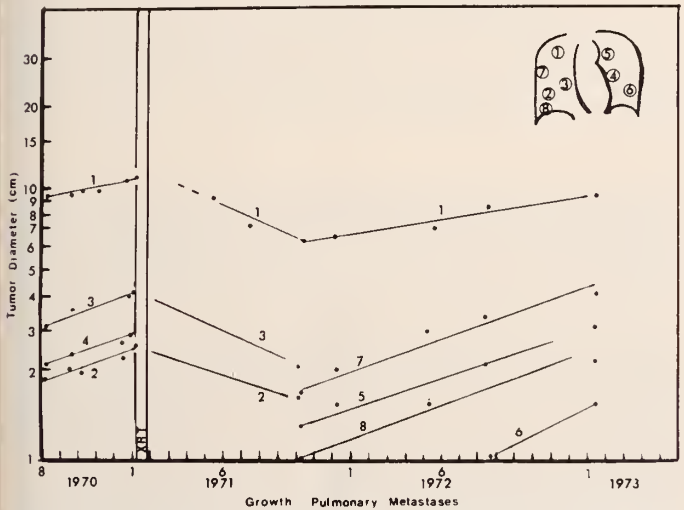

FIG. 2. The diameters of eight individual pulmonary metastases in patient B.K. are plotted on a semi-log graph. Each dot represents the tumor diameter measured on a teleroentgenogram. A straight line plot on a semi-log graph indicates exponential tumor growth.

were measured on three to five roentgenograms. None were in the field of previous irradiation (Fig. 2).

The relationship between the growth rate of a tumor and its duration can be approximated by backward extrapolation of the growth curve after it has been established by multiple serial measurements of tumor size. In this patient, the largest nodule, with a diameter of 9.2 cm, at first observation, had a calculated Td of 218 days. Assuming a constant growth rate, backward extrapolation of the growth curve places the earliest pulmonary implant 18 years before. This may appear irrational but unusually long growth periods from tumor inception to diagnosis have been postulated for other slow growing tumors including carcinoma of the colon and some fibrosarcomas (infra vida). Spratt and Ackerman report the growth rate of a colonic adenosarcoma observed by serial barium enemas for 7.5 years (10). They established an exponential growth curve and a doubling time of 636 days. By backward extrapolation, the inception of this tumor would have taken place some 52 years prior to diagnosis in a patient, aged 67 years. The growth rate of a large tumor may become retarded as its size increases (Gompertzian function) for a variety of reasons. Central necrosis may result from outstripping of the blood supply. Other factors include increased cell loss, a decrease in the fraction of proliferating cells, and alterations of host resistence (11). Assuming a slowing rather than constant growth rate, the duration of this primary nodule would have been even longer than the 18-year estimate based on a constant growth rate.

After a modest reduction in size in response to irradiation, nodule one resumed growth. Observation of tumor regrowth over a period of 180 days yielded a calculated Td of 257 days, slightly longer than the pretreatment Td of 218 days.

During this same period prior to irradiation, the diameters of three other nodules two, three and four in Table I were measured on serial chest x-rays and their growth curve plotted in Fig. 2. The diameters of these tumors were relatively small, ranging from 2 to 3.1 cm. The calculated Tds were 139, 126 and 145 days, respectively, averaging 137 days. Considering the relatively small size of these pulmonary nodules and their uniform growth rate, they would appear to be more suitable for biomathematical analysis.

Backward extrapolation of the growth curve would make the duration of these nodules approximately 11.2 years. This corresponds closely to the clinical sequence of events. Further confirmation was afforded by the postmortem examination; since there were no other foci of tumor that might have been a source of pulmonary metastases.

The patient survived a total of 14 years after amputation of a primary tumor. This represents 37 tumor volume doublings based on an average Td of 137 days; or, 23 tumor volume doublings based on the longest Td of 218 days. She survived seven Tds after discovery of pulmonary metastases. This did not exceed the lethal limit as defined by Spratt and Spratt, implying no therapeutic benefit from irradiation of her pulmonary metastases (4).

Growth Rate and Survival for Fibrosarcoma

The tumor doubling times (Td) for fibrosarcoma encompass a broad range, 11 to 274 days, in different reports (12, 13, 15). The Tds of 70 individual nodules (including 51 from the author's series) in 25 patients are represented in Figure 3. The cumulative relative frequency of the calculated Tds have been plotted successively on logarithmic probability paper. The distribution of Tds approximate a straight line, indicative of a log normal or Gaussian distribution. Growth rates tend not to be discontinuous; but rather, they display a continuous spectrum of growth from rapid to slow. A log-normal frequency distribution of randomly observed tumor diameters and tumor growth rates has been recorded for many tumors (10, 14, 15–20). It supports the concept that tumor growth of these pulmonary metastases is by geometric progression (3, 4, 16, 20, 21).

Survival data for 25 patients has been plotted in Figure 4. This is a select group because all ultimately died with disease. Survival has been recorded in both units of time, as well as in multiples of tumor volume doublings. Survival in time is the product of the growth rate (Td) and the number of tumor doublings the patient lives. Survival time, as a measure of the efficiency of a treatment technique, can be misleading as the duration of a patient's survival is influence predominantly by the rate of the tumor growth rather than the effectiveness of the treatment. This will be more obvious for a slowly growing tumor. In a previous study of the influence of growth rates on survival of patients with breast cancer who had recurrence in the mastectomy scar, there was a broad dispersion of survival times. The patients were then separated into three groups: rapid, intermediate, and slow tumor growth rate, based on the tumor volume doubling times. When survival was measured in multiples of tumor volume doublings, differences between each group were considerably narrowed. Division of the same population into two groups over and under five-year survival showed no differences when survival was measured in multiples of Tds (18).

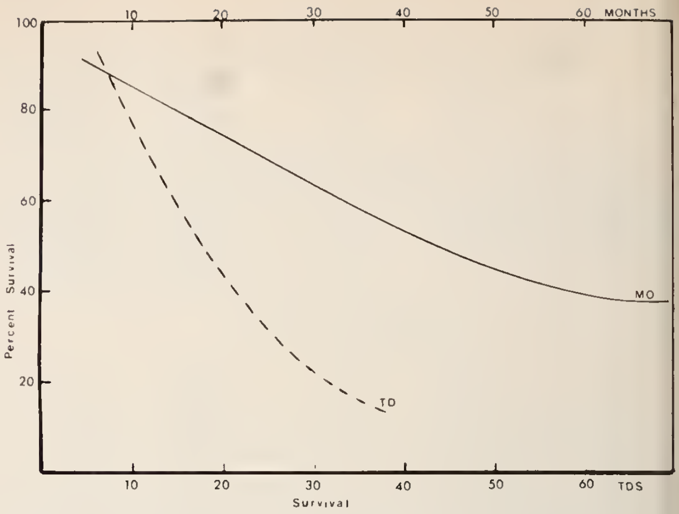

Fig. 4. Cumulative survival is recorded for the 25 patients in multiples of Tds (dotted curve) and in units of months (solid curve). There is a relatively narrow range of survival in Tds, with 80% falling between 10 and 50 Tds. When measured in chronological time there is a wide range of survival from one to 25 years. Fifty percent survived five years or longer.

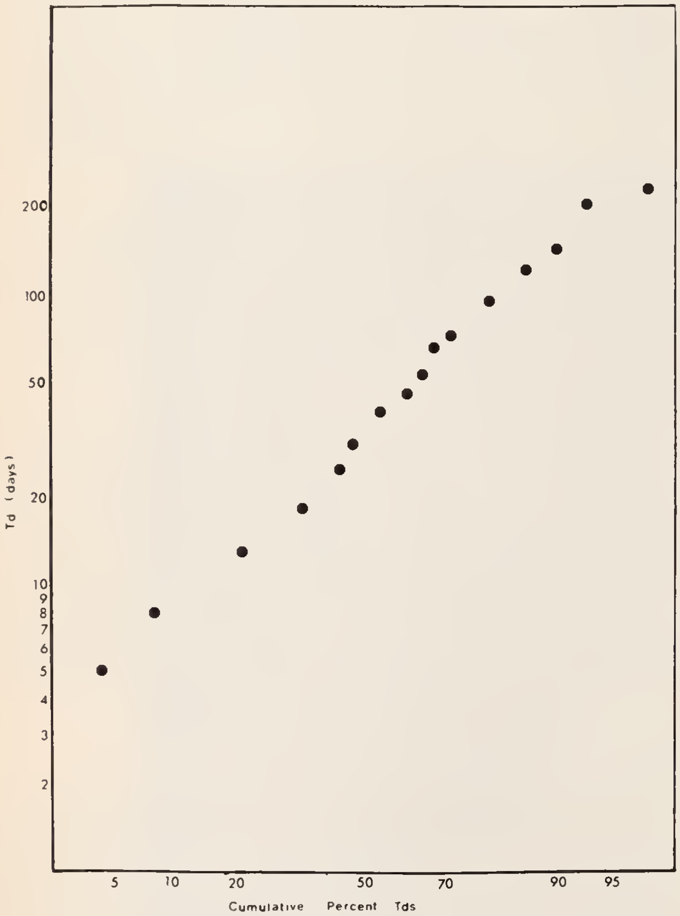

Fig. 3. The cumulative relative frequency of the calculated Tds have been plotted successively on logarithmic probability paper. There are 70 individual Tds derived from 25 patients. The distribution closely approximates a straight line, indicative of a log-normal or Gaussian distribution. A log-normal distribution of randomly observed tumor diameters and tumor growth rates supports the concept that tumor growth is exponential.

Survival for this group of fibrosarcoma patients encompasses a relatively narrow range when measured in multiples of Tds. Approximately 50% survived up to 20 Tds and 75% of the patients survival fell within 30 Tds. Survival times for the same cohort measured in chronological time ranged from one to 25 years. The generally slow growth rate of typical fibrosarcomas is reflected in the survival of half of the patients (12/25) for more than five years though all ultimately died with disease. The use of the Td as a yardstick of survival would thus appear to be a more realistic measure of the effectiveness of a particular treatment than units of time. Unless corrected for growth rate, survival statistics can be misleading.

Conclusion

The biomathematics of tumor growth were applied to one patient with long survival and late metastases, and to a select group of doomed patients with soft tissue fibrosarcomas. The duration of survival depended chiefly on the growth rate of the cells, i.e., tumor volume doubling time (Fig. 5). The same parameter of growth rate

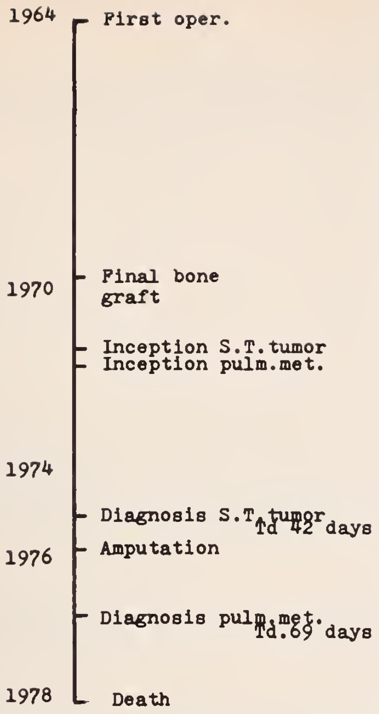

FIG. 5. A scatter diagram correlating survival in months with the Td of the individual tumor. There is a general trend toward increased survival time with slower tumor growth in this select group of patients, all of whom died with disease.

must be incorporated into an evaluation of the effectiveness of a specific treatment in prolonging the life of the patient.

The log-normal distribution of the rates of growth and of survival are indicative of the wide range of values that are characteristic of cancer. Malignant kinetics are probably the most significant single factor in prognosis (18).

Backward extrapolation of the growth curve to determine the time of inception of a metastasis is a clinically reasonable approximation and focuses attention upon the long silent preclinical interval during which occult metastatic spread may occur.

Prolonged observation, especially in patients with slow growing tumors, is mandatory.

Addendum

The biomathmatical analysis of tumor growth based on doubling time has been applied to a patient who was under continuous treatment. The therapeutic efficiency has been evaluated.

A white female, aged 45 years, had swelling of her elbow for 20 years. Over a six-year period, six biopsies of the ulna were performed with a histologic diagnosis of fibrous dysplasia and no evidence of malignancy. The last procedure was performed 4.5 years prior to her present admission. At this time, a soft tissue mass over the operative site, measuring 1.5 × 3.3 cm, was first discovered. During an eight-month period of observation, the diameters were measured on four sets of comparable radiographs of the elbow. These were plotted as areas on a semi-log graph and exponential tumor growth was established with a Td of 49 days. Backward extrapolation of the growth curve indicated that the inception of this tumor could have occurred four years prior to its discovery.

Biopsy and above elbow amputation revealed a poorly differentiated soft tissue sarcoma arising from a recurrent fibroosseous lesion (ossifying fibroma) with malignant changes in the bone as well. A prophylactic course of adriamycin, a total of 410 mgm, in five monthly doses, followed amputation. Eight months later the first pulmonary metastasis was diagnosed. Eight chest roentgenograms prior to this were normal.

The pulmonary metastasis was observed over a period of 197 days prior to irradiation. Serial measurements of the diameters of the nodule, plotted on a semi-log graph yielded an exponential growth rate with a Td of 69 days. By backward extrapolation of this growth curve the earliest microscopic implant in the lung could have occurred 5.6 years prior to its first diagnosis that would place the inception of the pulmonary metastasis soon after the inception of the soft tissue tumor (Fig. 5).

Subsequently and until her death, she received palliative CO60 irradiation to multiple metastatic sites including 4000 rads in 32 days to the pulmonary metastasis, and a second course of multiple drug chemotherapy (high dose methotrexate, vincristine, DTIC and cyclophosphamide).

The patient survived 49 months after the diagnosis of a soft tissue fibrosarcoma. This is equivalent to 21 tumor doublings based on the growth rate of the pulmonary nodule and falls into the 50 percentile survival for the entire group of patients all of whom died with disease and whose survival is recorded in Figure 4. She survived 24 months after first discovery of her pulmonary metastasis, equivalent to ten tumor doublings. This did not exceed the lethal limit as defined by Spratt and Spratt, implying no therapeutic benefit (16).

The sequence of events, for this patient, are illustrated in Figure 5, and the biomathematical analysis is superimposed. It suggests that microscopic metastases may be an early event occurring during the silent, preclinical period of tumor growth and may be close in time to the inception of the primary tumor. This has therapeutic implications and points up the ofttime general nature of neoplasms that appear clinically localized. As a parameter of therapeutic efficiency, survival measured in multiples of tumor doublings is more realistic since it eliminates the influence of growth rate on survival. This patient, despite a four-year survival, benefited little, if any, from the intensive therapy she received.

Acknowledgment

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Diverticulosis and Diverticulitis of the Colon*

RICHARD H. MARSHAK, M.D., ARTHUR E. LINDNER, M.D.,** AND DANIEL MAKLANSKY, M.D.

Colonic diverticula are outpouchings or protrusions of mucosa that develop through the muscular wall of the colon, forming sacs. These sacs are acquired rather than developmental in origin and are classified as false diverticula since they lack the full thickness of the bowel wall. From the clinical point of view, colonic diverticular disease is seen in two phases: 1) diverticulosis, which may be asymptomatic or associated with abdominal pain or rectal bleeding, and 2) diverticulitis, which implies inflammation of diverticula and usually perforation. We will discuss separately the roentgen findings in each of these aspects of diverticular disease, but it is important to remember that overlap does occur. The radiologic findings must always be interpreted in relation to the clinical aspects of each patient.

Diverticulosis

The incidence of colonic diverticula increases with the age of the subjects studied. Diverticula are rare in patients below the age of 30, but it can be demonstrated in perhaps half of patients over 60 years of age (1).

Diverticula are most frequently found in the sigmoid, but they can be seen in any portion of the large bowel except the rectum. Those on the right side of the colon tend to have wider and shorter necks. Diverticula may be solitary lesions, be present in moderate numbers or, be multiple, as in massed diverticulosis. In this last instance, the entire contour of the bowel is effaced by a large number of diverticula indentified as grapelike structures.

Diverticula vary considerably in size, some so small that they resemble a tiny dimple; others may enlarge to sac-like structures 2 cm or more in diameter. Fecaliths are often found in diverticula, especially in the sigmoid.

When specimens of involved colon are studied, the sacs are found to arise from the walls of the intestine in four rows, one on each side of the mesenteric taenia and one on the mesenteric side of each of the antimesenteric taeniae (2). The mucosa appears to herniate at the sites where blood vessels penetrate the wall of the bowel.

Pathologic studies have demonstrated that mural muscle thickening is an important concomitant of diverticulosis (3, 4). This morbid finding is associated with clinical observations of increased intraluminal pressure in patients with diverticula (5). Such studies have led to the now widely held hypothesis that the colon in patients disposed to diverticular disease tends to form segments with increased pressure (in comparison to normals) in response to food, emotional stimuli, and cholinergic drugs. Such high pressures are associated with muscle hypertrophy and with the pulsion forces that cause diverticula to be extruded (5). A high bulk diet, that tends

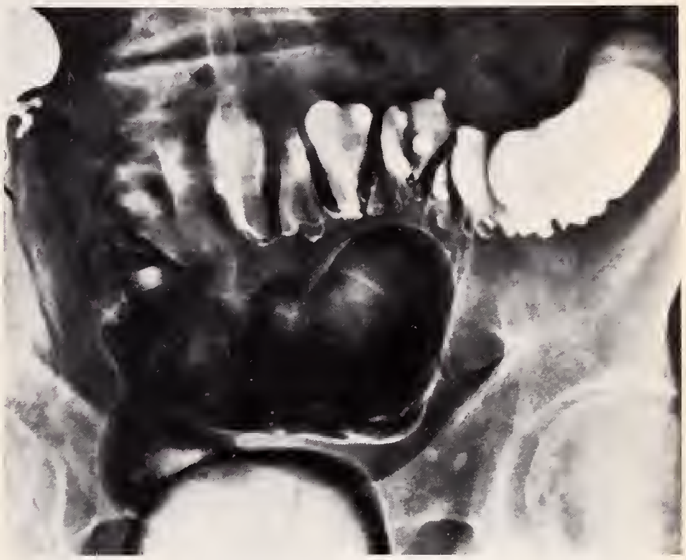

Fig. 1. Diverticula of the colon. Air contrast study. Spot film of the sigmoid reveals scattered diverticula seen as small outpouchings of mucosa containing barium. The diverticula are seen in profile and face-on.

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From the Department of Radiology, Mount Sinai School of Medicine and ** the Department of Medicine, New York University School of Medicine, New York, N.Y.

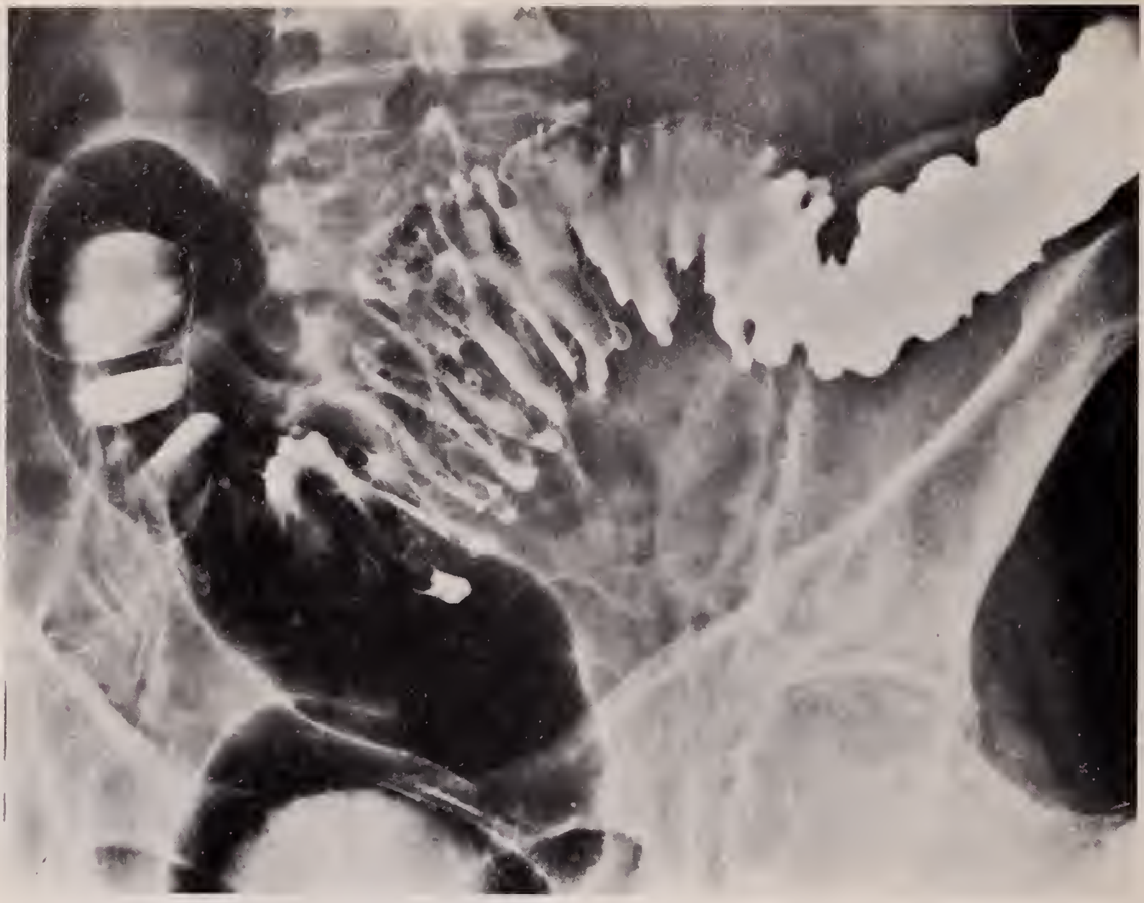
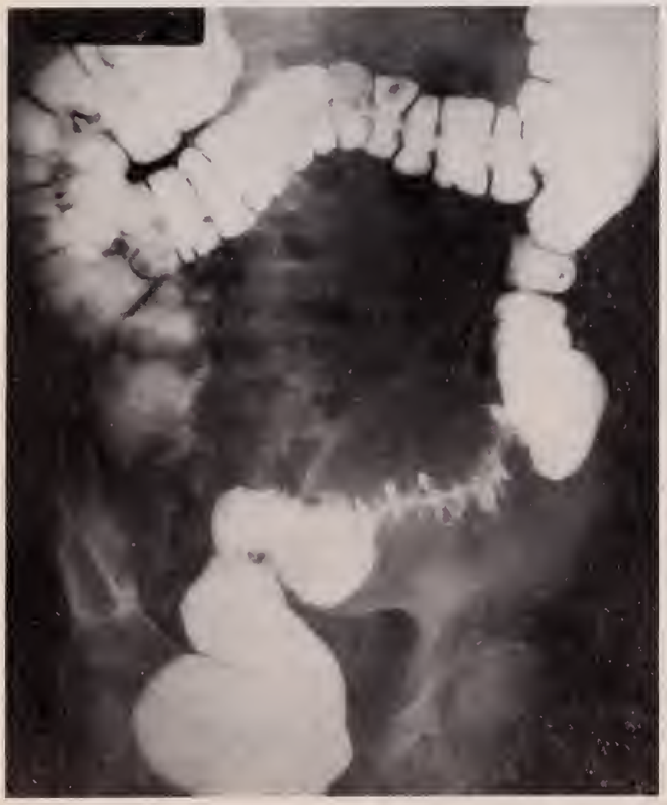


FIG. 2. Diverticular disease of the colon. A moderate number of diverticula, with slight shortening and limitation of distensibility of the colon.



to decrease intrasigmoidal pressure, has been advocated in the treatment of diverticular disease, and anticholinergic drugs may be beneficial (6).

Patients with diverticulosis are often asymptomatic, the sacs discovered only during a routine roentgen examination. In other patients the involved segments of bowel are spastic and painful, a clinical syndrome that mimicks, and confuses the diagnosis of, the irritable bowel syndrome (7). Such pain and spasm may occur in the absence of diverticula, when only muscle thickening can be demonstrated, and this has been referred to as the "prediverticular state". Surgical myotomy, although not widely employed, has been advocated by some authorities in the management of colonic pain associated with muscle hypertrophy and diverticulosis (8). For the great majority of patients with symptomatic diverticulosis, effective treatment is offered by a high residue diet, bulk-forming medications such as hemicellulose or psyllium seed, and judicious use of anticholinergics.

Bleeding may occur in diverticulosis, probably from erosion of vessels at the base of a diverticulum. The

FIG. 3. Diverticulosis. There are a large number of diverticula of the sigmoid associated with shortening and lack of extensibility and distensibility of the colon.

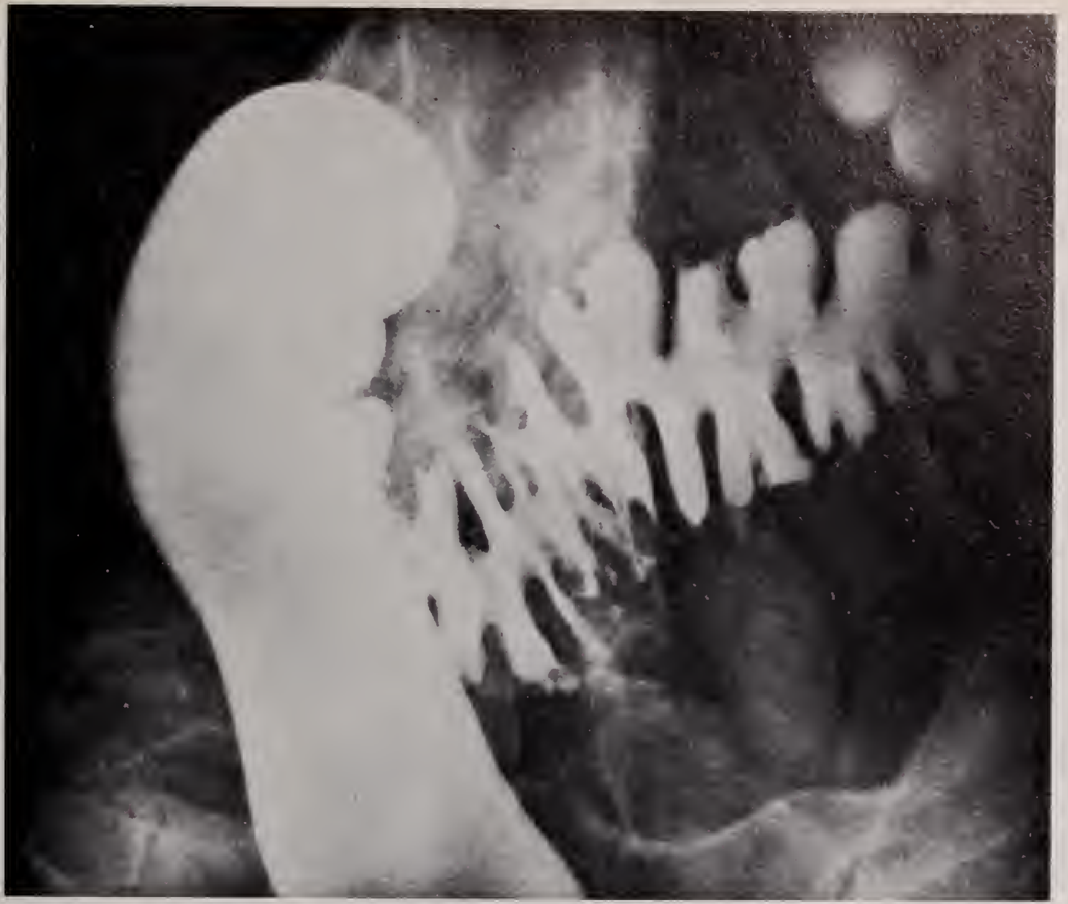


FIG. 4. Shortening of the sigmoid colon with concertina-like effect.

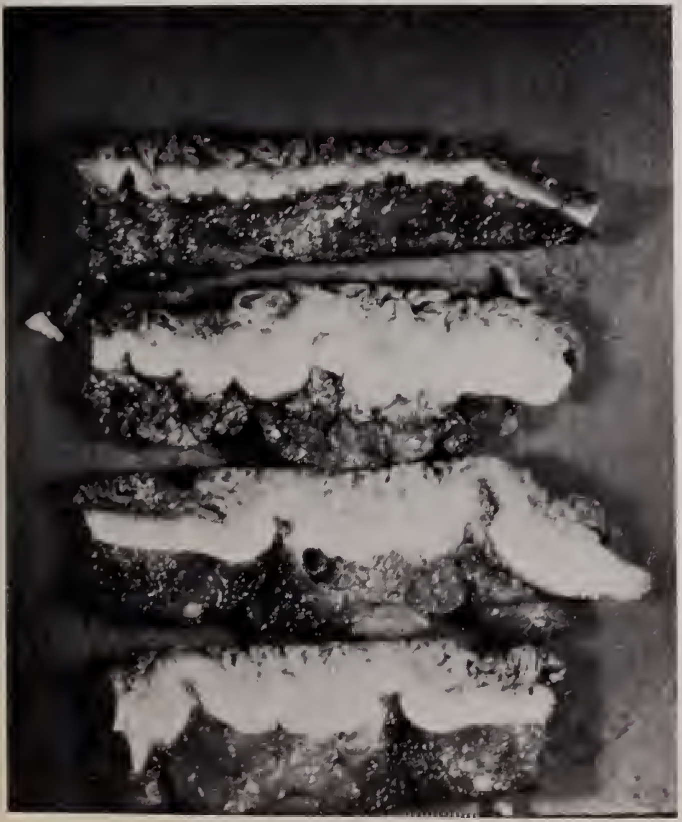


FIG. 5. Sections of normal colon and sections involved with diverticulosis. The top section illustrates the normal thickness of the muscularis layer of the colon. The lower three sections demonstrate the marked thickening of the muscularis associated with diverticular disease. The thickened muscle appears as a broad white band.

severity may range from mild hematochezia to massive hemorrhage. Clinical observations have emphasized the importance of ruling out other colonic lesions, especially carcinoma, before ascribing rectal bleeding to diverticulosis.

Roentgen Findings in Diverticulosis

The diagnosis of diverticulosis is best established by barium enema examination. Small numbers of diverticula do not distort or alter the configuration of the bowel (Fig. 1). Larger numbers of diverticula, however, may produce shortening of the colon or alterations in distensibility and motility (Fig. 2).

The muscle hypertrophy that accompanies diverticulosis may produce a variety of bizarre radiologic configurations. Shortening of the bowel or lack of distensibility frequently accompany diverticulosis (Fig. 3). The shortened bowel causes a concertina-like appearance of the mucosa (Fig. 4). In the past it had been suggested that the cause of the bowel shortening in diverticulosis

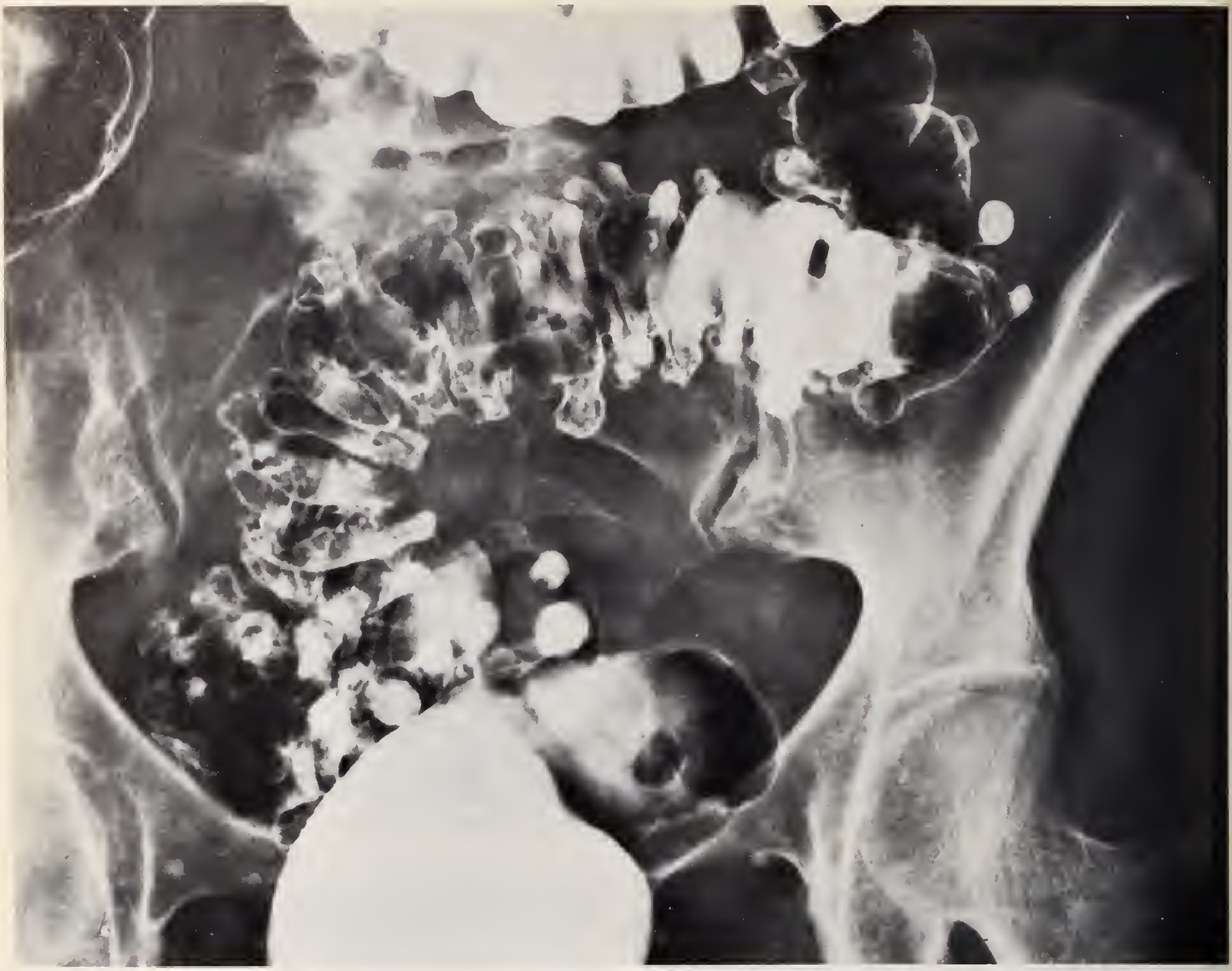


FIG. 6. Multiple-massed diverticulosis.

was simply the entrance of mucosa into multiple diverticula. More recent pathologic studies, however, make it more likely that mural muscle hypertrophy is the cause of the shortening phenomenon (Fig. 5).

The roentgen appearance of massed diverticulosis, with multiple grapelike structures, presents a distinctive appearance (Fig. 6). It should be noted that a small carcinoma or a polyp can easily be hidden in massed diverticulosis. A clinical situation such as rectal bleeding may require several barium enema examinations or colonoscopy for adequate study of the involved area.

Diverticulitis

Diverticulitis is an inflammation of the lining of a diverticulum. This lining consists only of mucosa and perhaps some submucos. Localized perforation occurs often and can be single or multiple. It results in intramural abscess that is almost immediately confined by adhesions (Fig. 7, 8). On rare occasions the perforation enters the general peritoneal cavity.

Occasionally a barium enema examination is performed during the stage of acute diverticulitis and the perforation of the diverticulum may be identified (Fig. 7). Delayed films obtained after evacuation help demonstrate this perforation. More frequently, of course, the patient is examined radiographically during the subacute phase of the disease (9). The abscess produced by the perforation has been confined by adhesions and produces an intramural defect (Fig. 9). The diverticula adjacent to the intramural defect are spastic, irritable, thinned, empty of fecaliths, and attenuated. These diverticula frequently "drape" over the abscess ("drape sign") (Fig. 10, 11).

There also may be a spreading cellulitis adjacent to the abscess involving many diverticula. Both the abscess

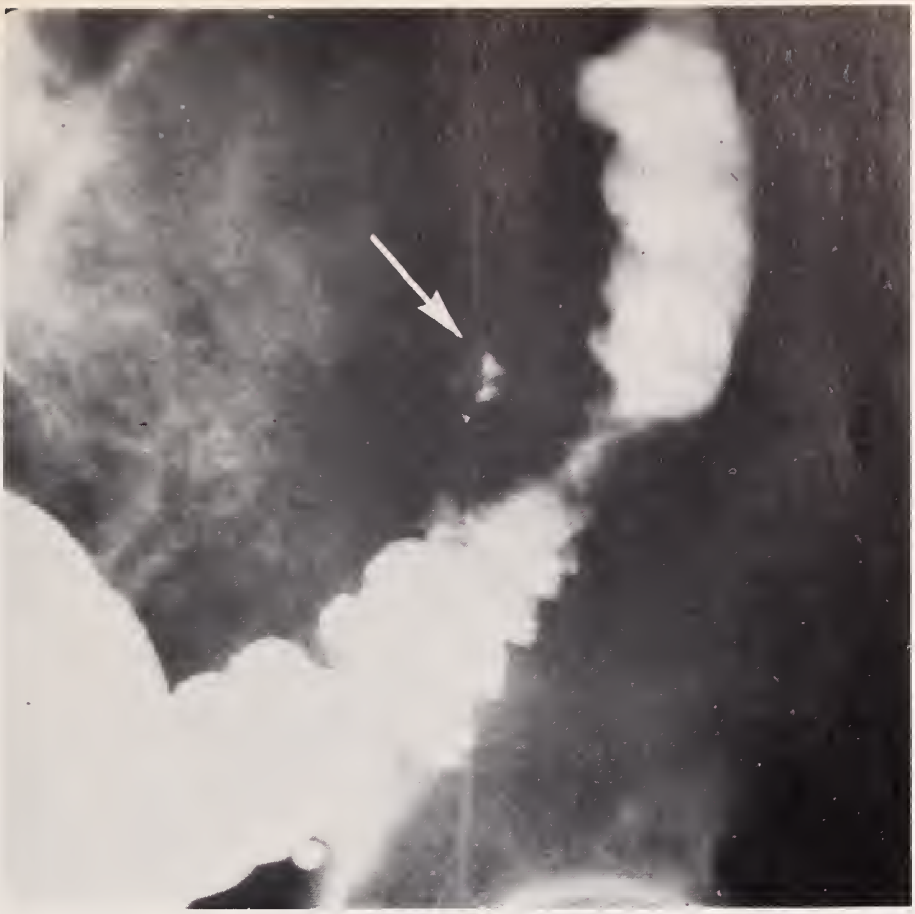
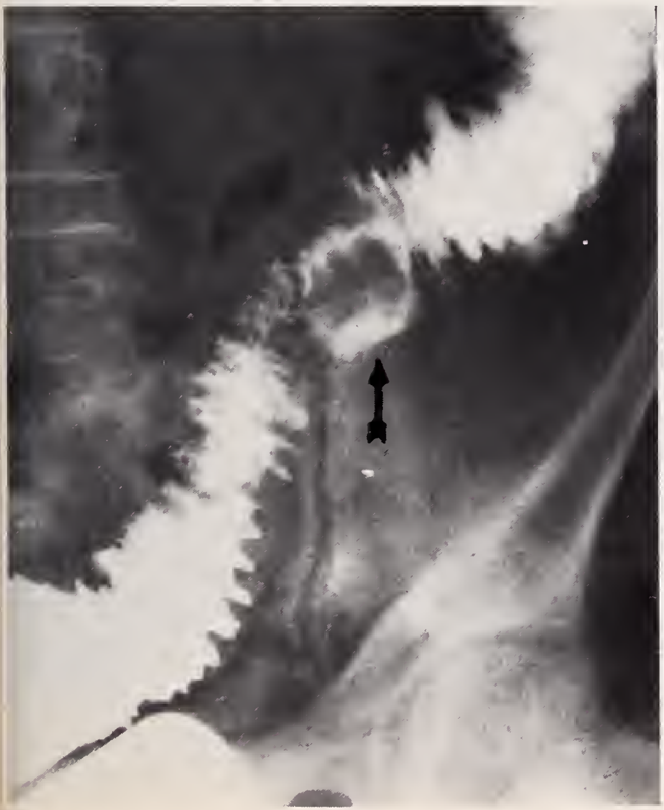


FIG. 7. Diverticulitis. There is a tiny perforation associated with a short segment of narrowing.



and the involvement of adjacent diverticula produce additional roentgen alterations consisting of spasm, irritability, shortening, narrowing, rigidity, distortion and thickening of the folds (Fig. 12).

Diverticulitis most frequently involves a short segment of bowel (4-5 cm) but more extensive alterations (10-12 cms) are not uncommon (Fig. 12). The length of the inflammatory process depends, of course, on whether single or multiple diverticula perforate and on the number of diverticula secondarily affected by their proximity to the perforation (Fig. 13).

Diverticulitis may resolve completely (Fig. 14 a,b,c). It has been our observation during the last several years that resolution of diverticulitis is more common than had previously been noted. This improvement may be the result of more vigorous and effective use of antibiotics. It is remarkable to observe the subsidence of many of these inflammatory processes with serial barium enema studies.

In some patients the inflammatory process persists and worsens. Such progression may be related to continued or subsequent perforation, to the development of fibrosis,

FIG. 8. Diverticulitis. There is a perforation with a small intramural abscess. Such abscesses are quickly confined by adhesions, preventing the spread of peritonitis.

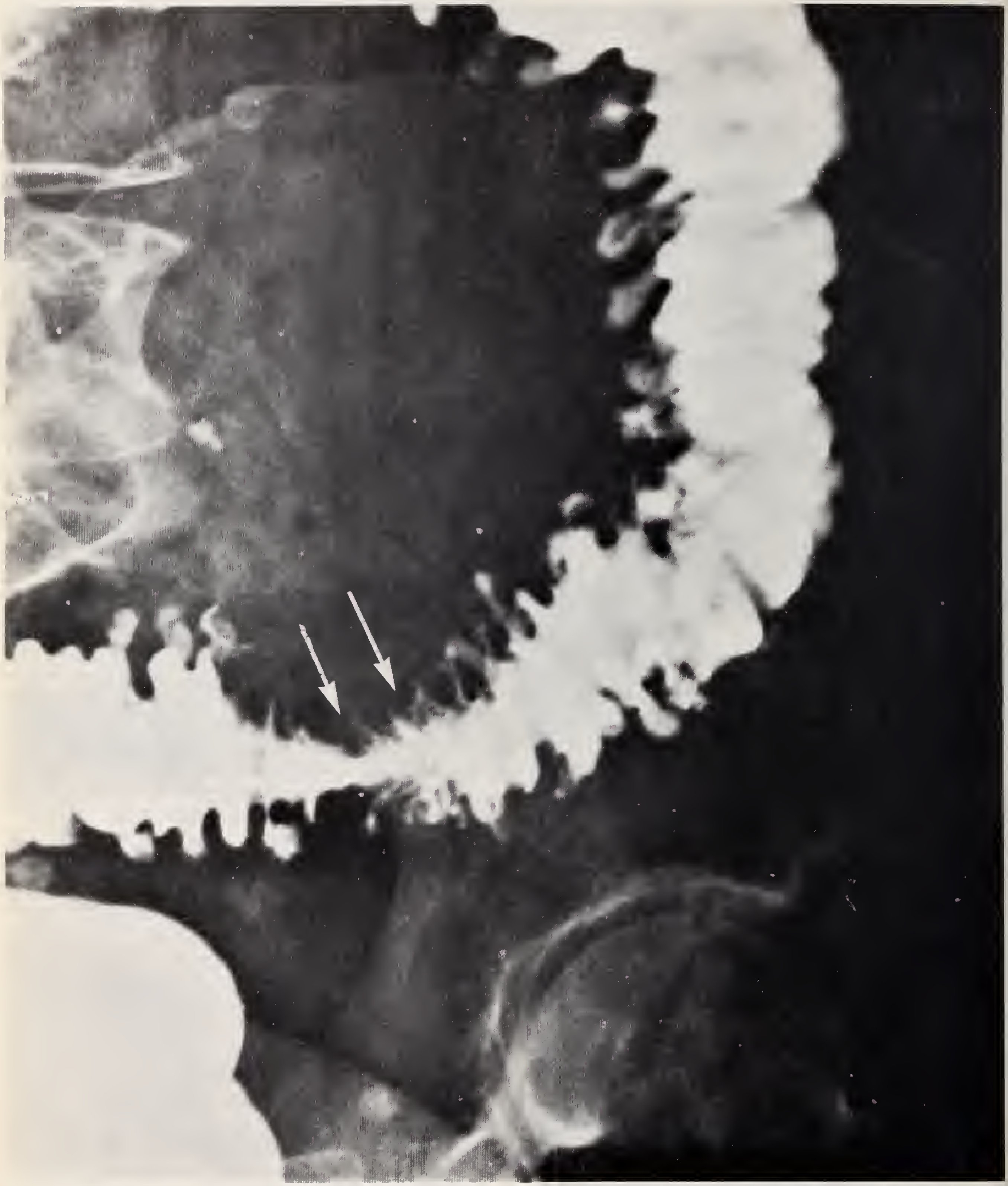


FIG. 9. Diverticulitis. Intramural abscess. The adjacent diverticula are beginning to overhang the intramural defect.

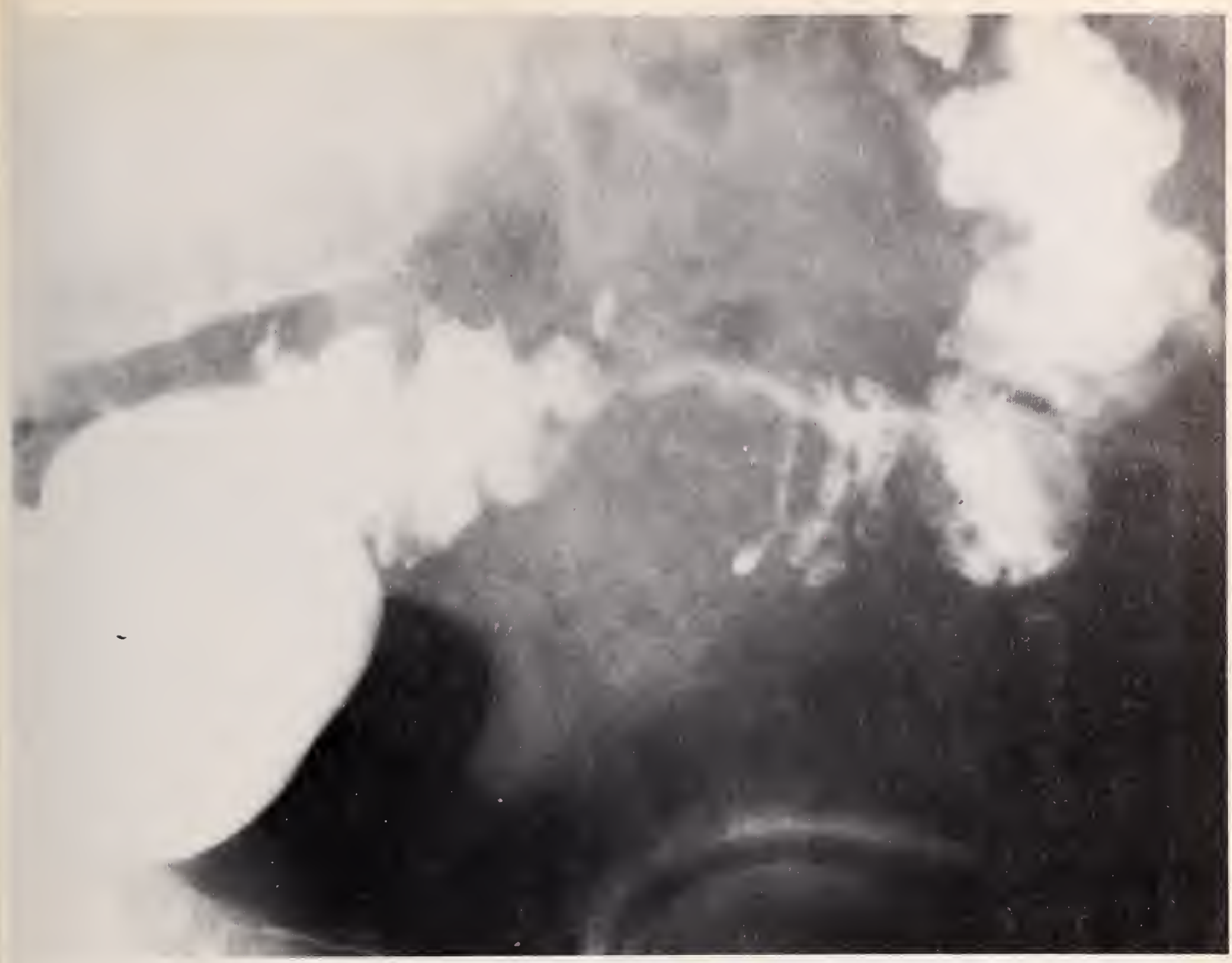


FIG. 10. Diverticulitis. Intramural granuloma. The diverticula are draped over the defect.

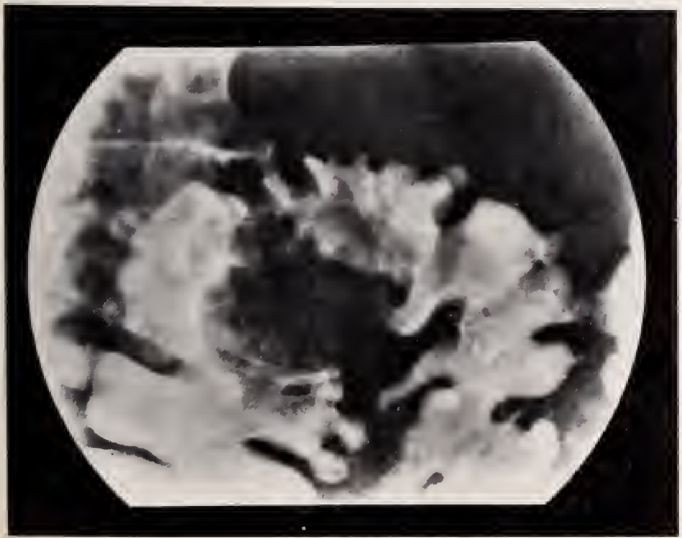


FIG. 11. Carcinoma of the colon. There is a marked narrowing, an eccentric lumen, and overhanging edges in association with diverticula. The overhanging edge should not be confused with the drape sign seen with the granuloma in diverticulitis.

and to lack of response to antibiotics. In this chronic stage, the lumen becomes progressively stenotic, the bowel wall more rigid, and the intramural defect larger and more constant. As obstruction supervenes, differentiation from carcinoma becomes more difficult (Fig. 15). Finally complete stenosis occurs producing retrograde obstruction.

An intramural abscess may simulate the contour defect of colon carcinoma. However, the latter is easily differentiated at this stage by the lack of spasm and irritability (Fig. 9–11). When diverticulitis becomes more chronic, with severe narrowing of the bowel lumen, more difficulty in differential diagnosis is encountered. The importance of demonstrating an intact mucosa is paramount and this can be done only by multiple spot films during fluoroscopy. Irregularity of the contours, an eccentric lumen, ulceration of the mucosa, overhanging margins and an irregular ledge favor the diagnosis of a carcinoma (Fig. 15). In the presence of considerable retrograde obstruction, demonstration of the proximal as well as the distal

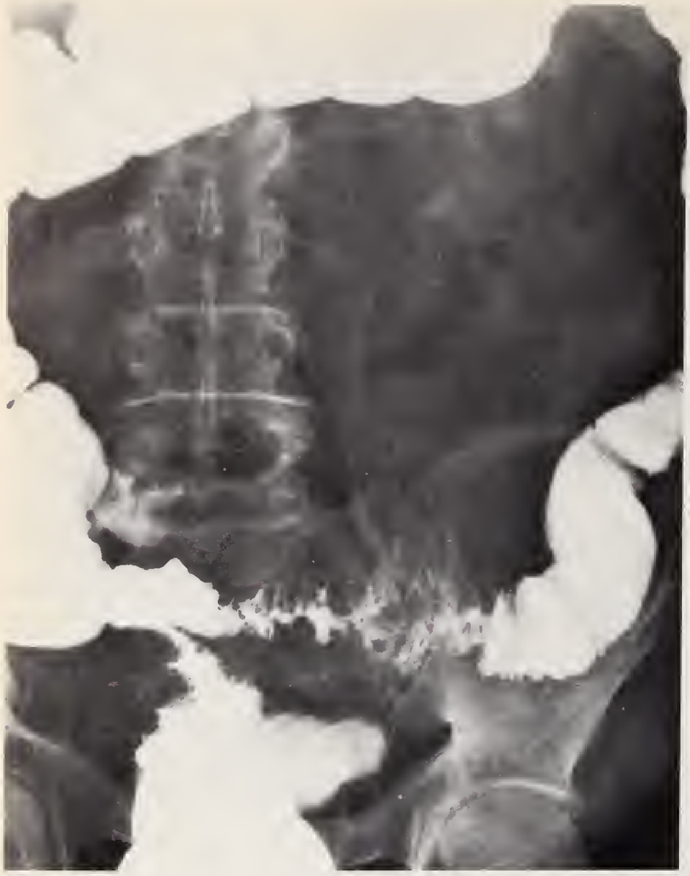


FIG. 12. Diverticulitis involving a long segment of sigmoid.

margins of the lesion is important. If this cannot be accomplished, differential diagnosis between diverticulitis and carcinoma may be impossible.

Fistulas and Sinus Tracts

In the early stages of diverticulitis, following localized perforation and abscess formation, sinus tracts and fistulas are not common. As the process becomes more chronic, short fistulous tracts extending from the diverticular sac, usually on the mesenteric wall, can be identified. These paracolic tracts are usually short but can be long (Fig. 16–18, 19a, b). They are sometimes bilateral and may extend into the urinary bladder. Rarely do they communicate with adjacent viscera.

Paracolic fistulous tracts are also seen in Crohn's disease of the colon, especially in association with diverticula (10). Granulomatous colitis can occur in middle aged and elderly patients and may affect any segment of the colon. In these age groups diverticulosis also is found often and so the two diseases may coexist (11). The clinical and radiologic differential diagnosis between segmental granulomatous colitis and diverticulitis may, therefore, be difficult (Fig. 20, 21 a, b, c, 22 a, b, c, 23). We have found the following features useful in distinguishing diverticulitis from Crohn's disease of the colon (Table I). Granulomatous disease may also involve several diverticula producing an associated diverticulitis (12). It is interesting to speculate whether or not the bowel that is weakened by diverticula is more susceptible to Crohn's disease.

Right Sided Diverticulitis

Changes caused by diverticulitis on the right side of the colon on barium studies are uncommon because chronic diverticulitis in this region is rare and because the patient with acute diverticulitis is usually explored as a surgical emergency without prior roentgen examination. The barium enema examinations that are availabile for study have been performed upon patients with low-grade acute diverticulitis or after exploratory laparotomy. The findings to be described are essentially those of a subacute stage. The roentgen findings consist of 1) a discrete, localized, intramural type of filling defect, 2) a longer eccentric area adjacent to the discrete defect, exhibiting limited distensibility, 3) contour changes manifested by coarsening of mucosal folds, irregular distention during filling and irregular emptying at evacuation, 4) local fixation of the involved portion of the bowel and 5) intact mucosal pattern and absence of any constant intraluminal filling defects.

A discrete eccentric defect is the result of inflammatory changes in the blocked diverticulum. The longer area of limited distensibility represents spread of inflammation

TABLE I

Granulomatous Colitis and Diverticulitis

Roentgen Features That Usually Distinguish Granulomatous Colitis From Diverticulitis

Diverticulitis	Granulomatous Colitis
Length of lesion usually short (3-6 cm) on occasion long; usually in sigmoid	Length of lesion usually long (10 cm or more); on occasion short, anywhere in colon
Diverticula sharply defined; often contain a fecalith	Abscess triangular with cap-like configuration; does not contaion a fecalith
Diverticular abscess has an intramural defect or an arcuate configuration of stretched folds	Folds are thickened and edematous; increased secretions present
No transverse fissures; folds usually have arcuate configuration. Stepladder effect not frequent	Transverse fissures and mucosal edema produce a stepladder configuration
Short pericolonic sinus tract	Long sinus tract; may be intramural or pericolonic
Mucosa normal	Mucosal ulcerations or cobblestoning

(Marked spasm and irritability and narrowing may prevent an adequate study of the mucosal pattern.)

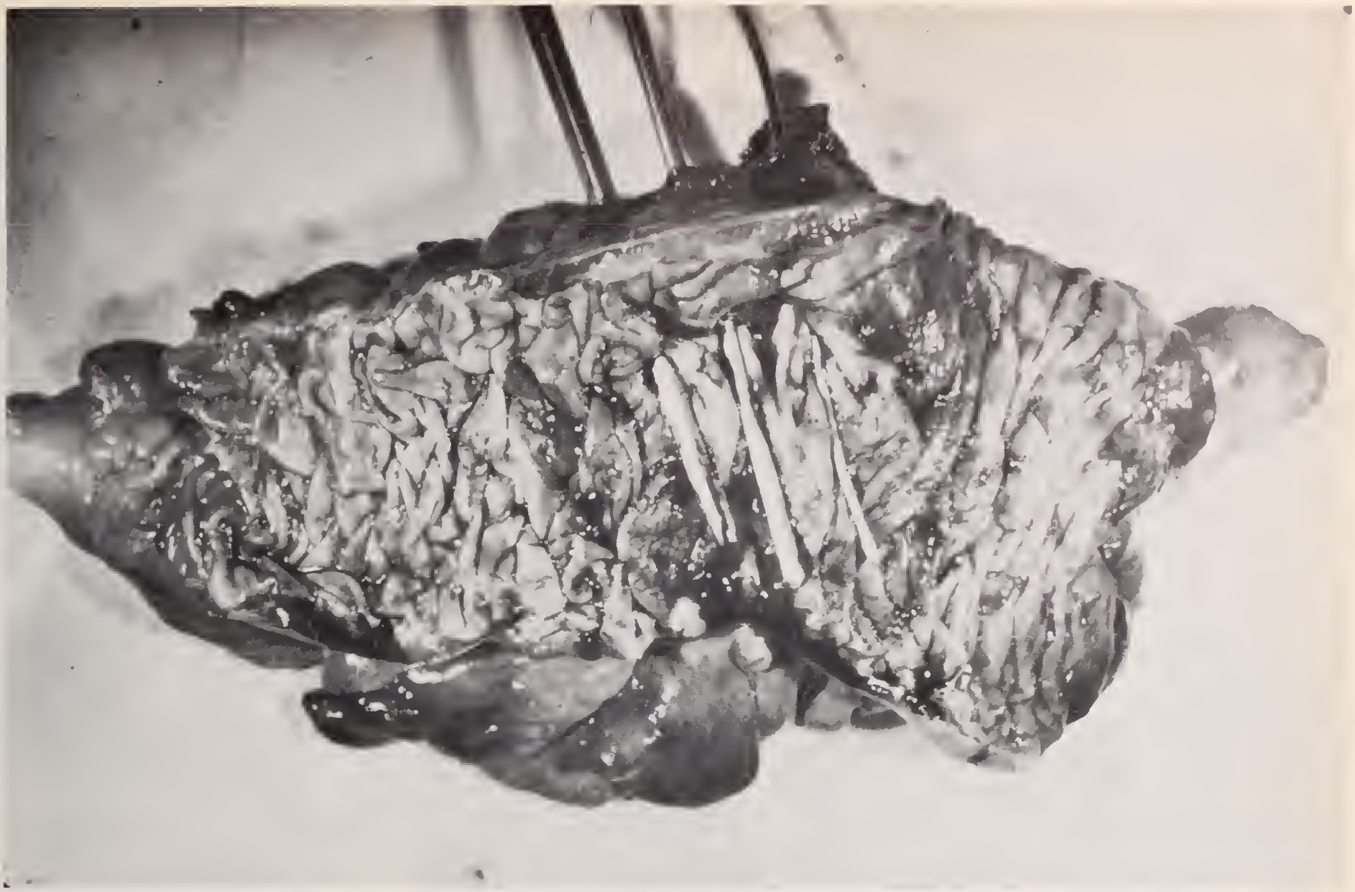


Fig. 13. Specimen of diverticulitis illustrating three perforations of diverticula. Three metallic probes are passed through the perforated diverticula. The mucosa has an accordian-like appearance.

of lesser severity in the wall of the bowel. Unlike the situation in the left side of the colon, incisuras at any point in the ascending colon that remain fixed and stationary are indicative of an inflammatory process (Fig. 24). There is no irregularity of the contours, which remain smooth. A soft tissue density or mass may be seen adjacent to the flat contour of the serrated bowel. This thickening may extend as far as the proximal transverse colon, usually along the lateral contour of the bowel. On evacuation studies, the transverse diameter of the collapsed bowel may be surprisingly wide. The mucosal pattern is thickened, irregular and sometimes associated with increased secretions due to inflammatory edema.

The large area of diminished distensibility, the lack of a filling defect, intact mucosal pattern, and the soft tissue density along the contour of the bowel are features that distinguish this lesion from a carcinoma. The roentgen appearance following antibiotics may return to normal. Right sided diverticulitis should be distinguished from acute appendicitis, granulomatous colitis, foreign body perforation, ischemic colitis and carcinoma.

Technique and Timing of the Barium Enema Examination in Diverticular Disease

Although a perforated carcinoma may simulate diverticulitis, there is no urgency in performing a barium enema examination at the onset of symptoms. Antibiotics are available for treatment on the basis of clinical findings. The acute stage of diverticulitis, with a localized perforation of the involved diverticulum, is thus not usually demonstrated radiographically. The clinician need not be concerned about the risk of barium enema as soon as acute findings subside. Containment of the acute abscess begins almost immediately and it is safe to perform a barium enema examination seven to fourteen days after the onset of treatment. Fluoroscopy with multiple spot films utilizing the full-column barium technique will demonstrate a perforation more readily than double contrast air studies, and it is a safer procedure (Fig. 7). Utilizing the full column technique, the course of the barium flow can be immediately determined fluoroscopically. The use of glucagon (1 mg intravenously) during

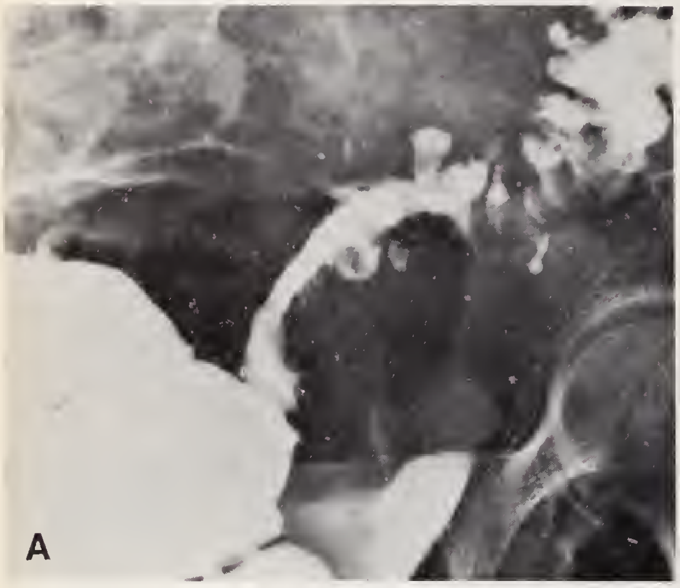


FIG. 14a. Diverticulitis. There is a large intramural abscess involving the sigmoid.

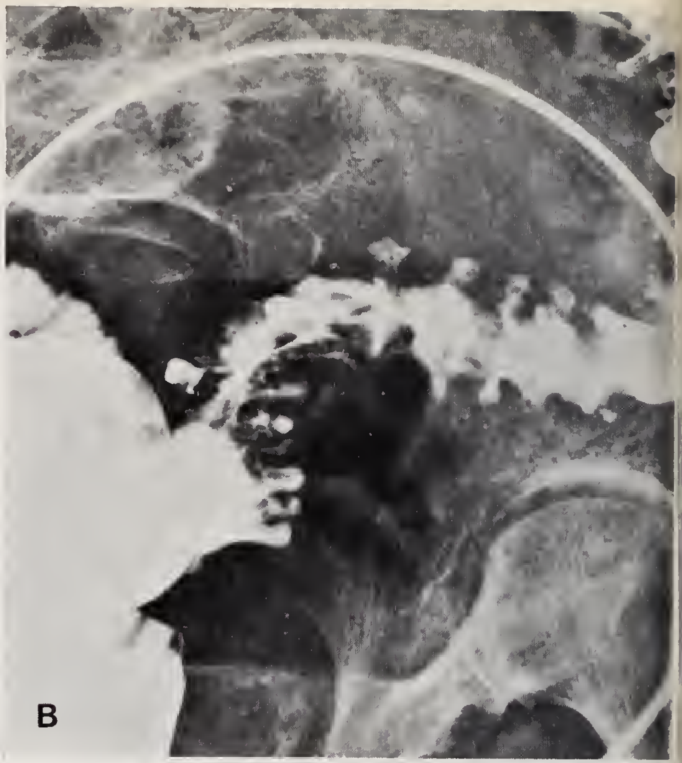


FIG. 14b. Diverticulitis–same patient as 14a two weeks later. The patient has been treated with antibiotics. The intramural abscess is half the previous size. There is some restoration of the narrowed lumen.

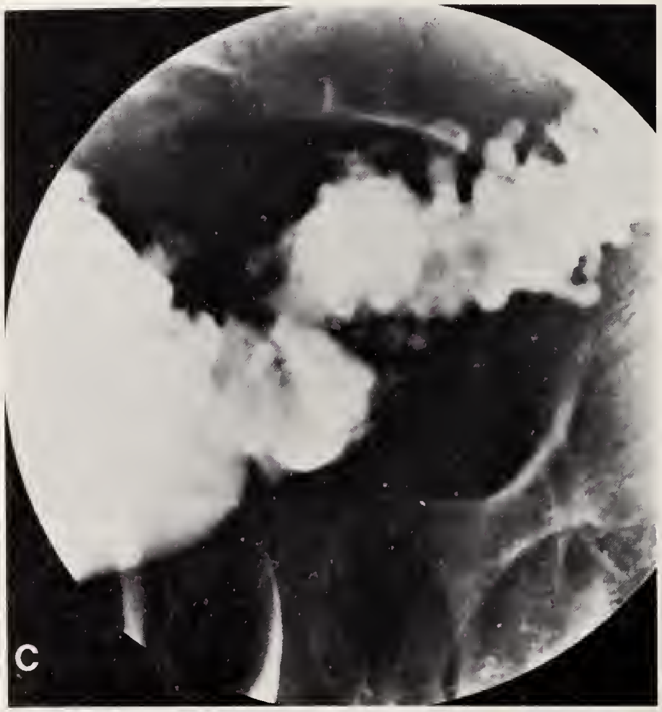


FIG. 14c. Diverticulitis. There has been almost complete resolution of the roentgen findings.

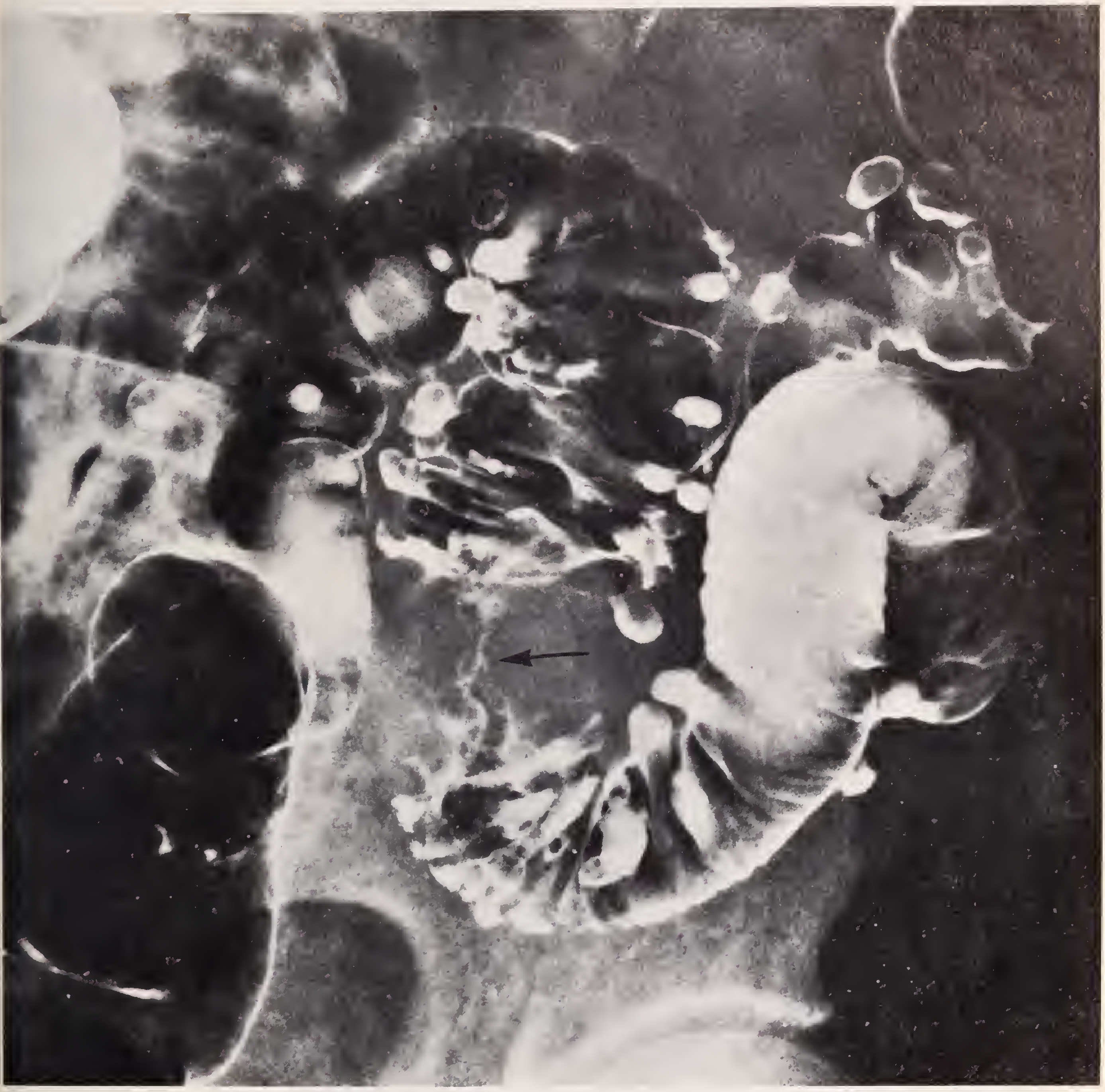


FIG. 15. Carcinoma of the sigmoid in association with multiple diverticula.

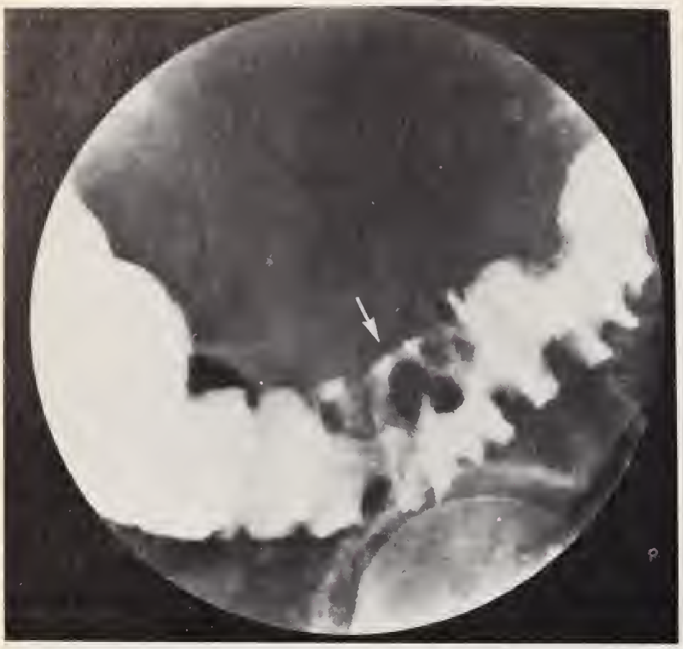


FIG. 16. Diverticulitis. There is a short fistulous tract on the medial aspect of the sigmoid. In the absence of the tract, it would be difficult to make this diagnosis.

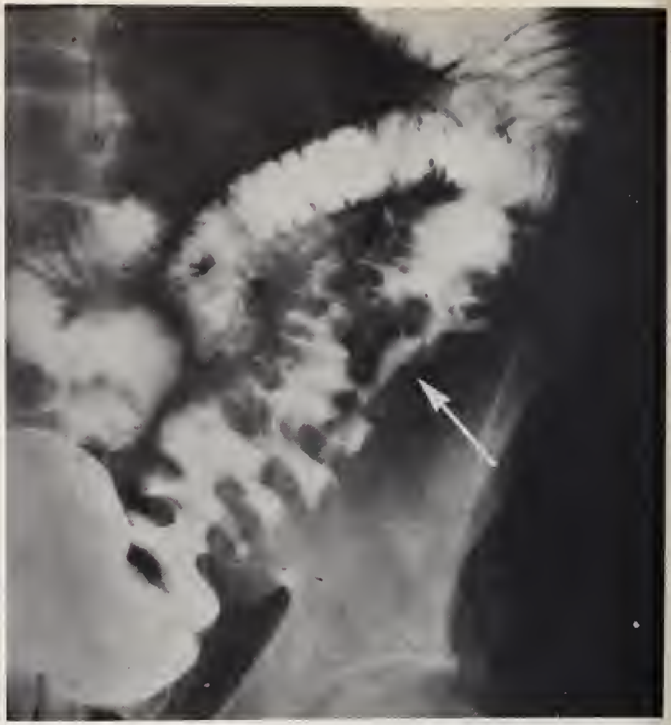


FIG. 17. Diverticulitis with two tracts.

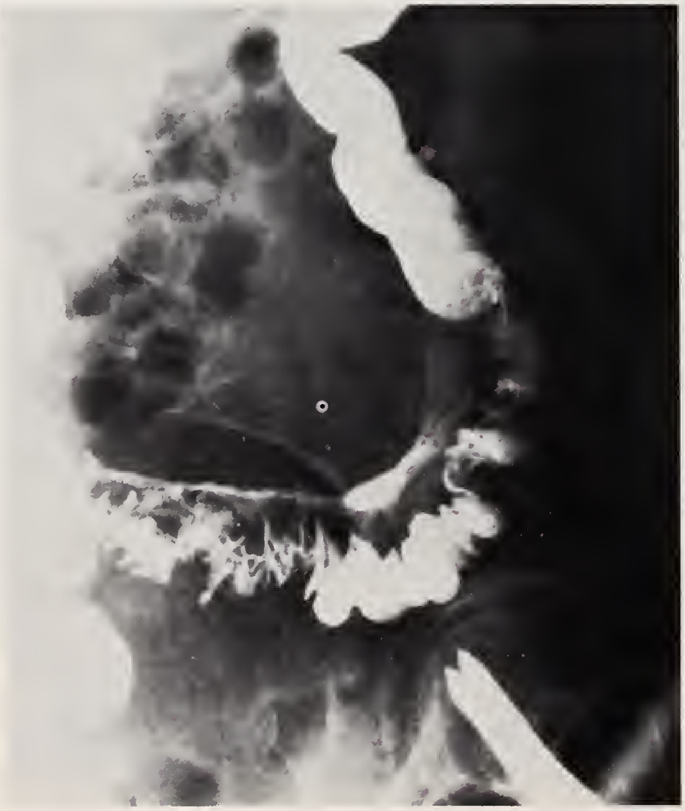


FIG. 18. Diverticulitis with long tract. The mucosa is minimally distorted.

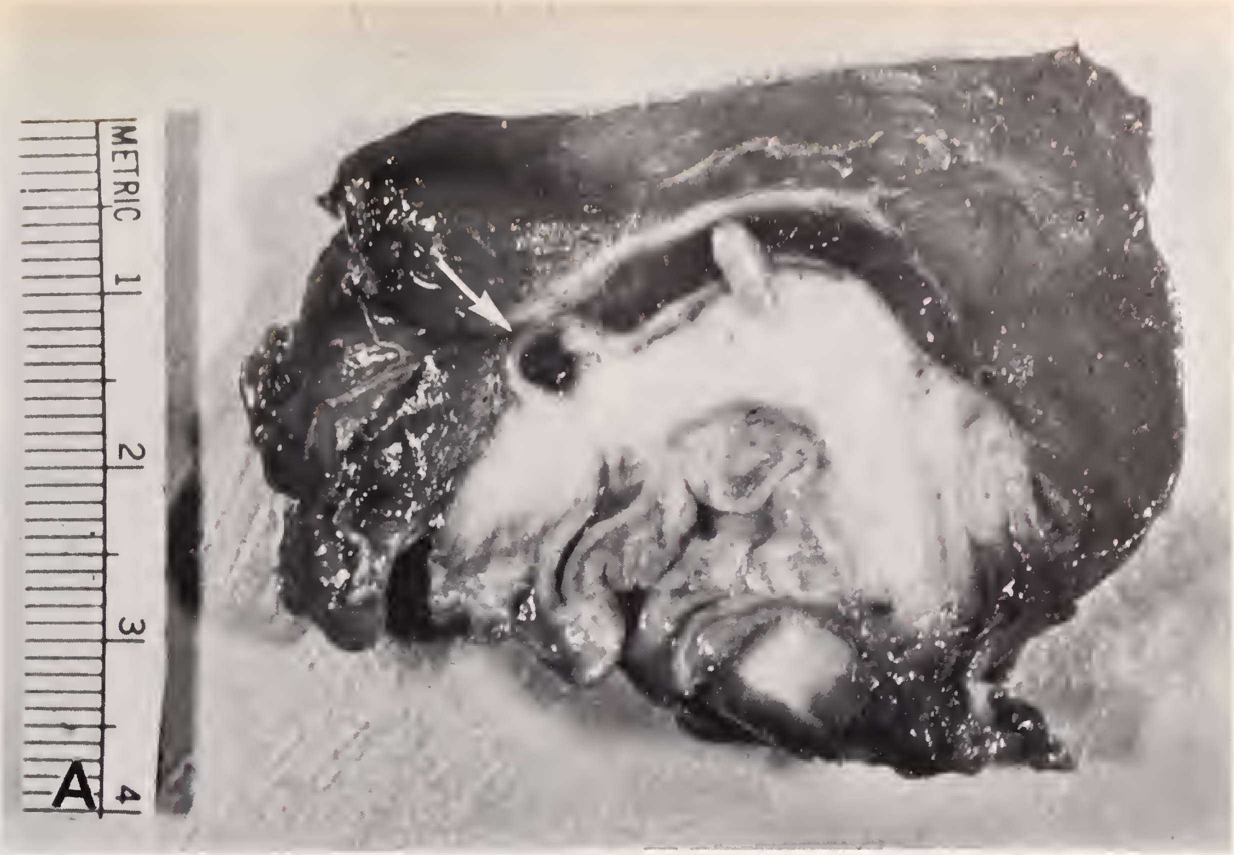


FIG. 19a. Diverticulitis perforating into a paracolic tract. Section of sigmoid colon. The mucosa is thickened (inferior). The muscular layer is thickened and appears as a broad white band. A small dark circular structure is seen at 10 o'clock. This represents a diverticulum (arrow) perforating into a paracolic fistula which encircles the thickened muscularis. The overlying serosa is inflamed.

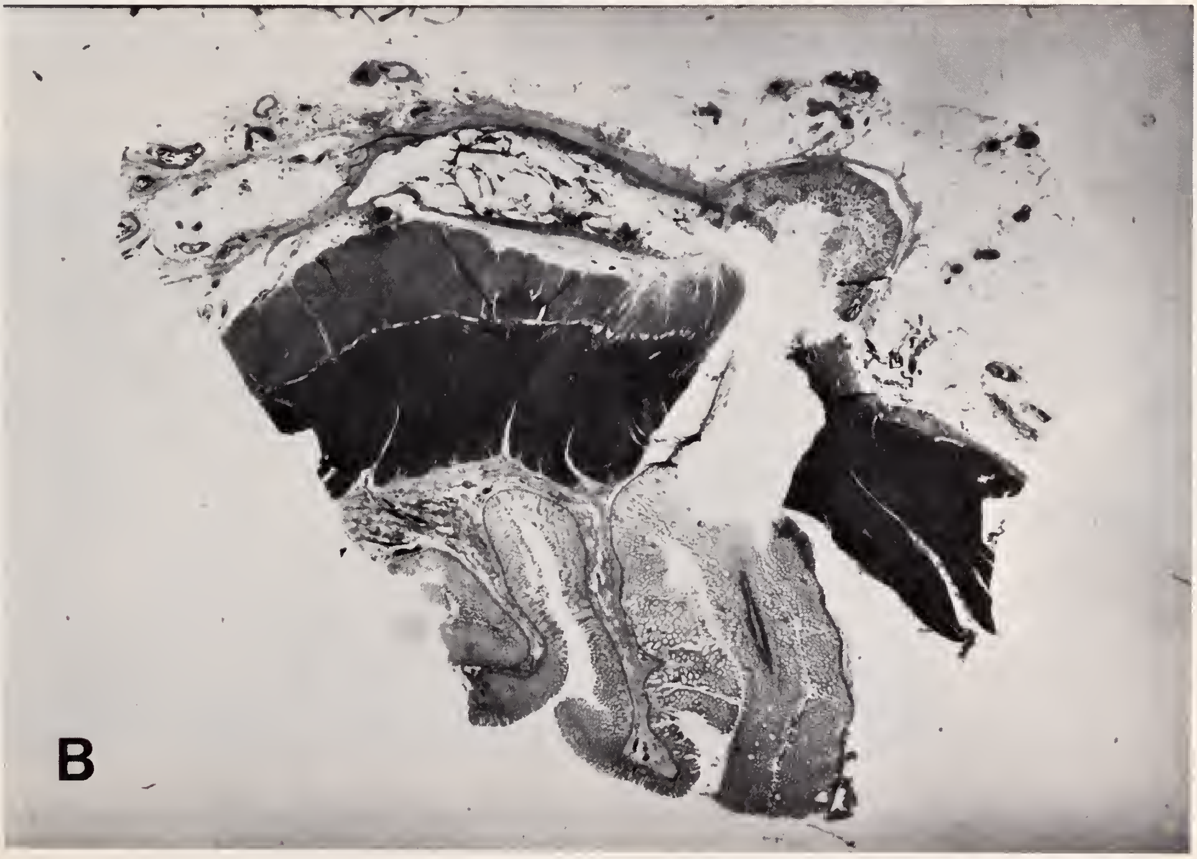


FIG. 19b. Low power photomicrograph of 19a.

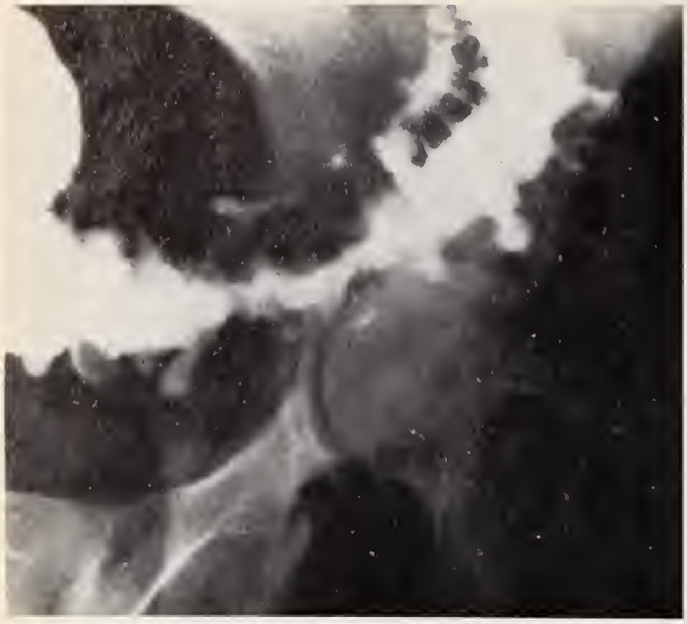


FIG. 20. Crohn's disease of the colon. There is a long fistulous tract situated in the medial wall of the sigmoid. Multiple diverticula are identified. There are several rounded sacs that could be due to abscess formation. Presumably when a segment of colon containing diverticula becomes involved with Crohn's disease the transverse fissures can easily penetrate the diverticula, producing diverticulitis, a step-ladder configuration and a paracolic fistula.

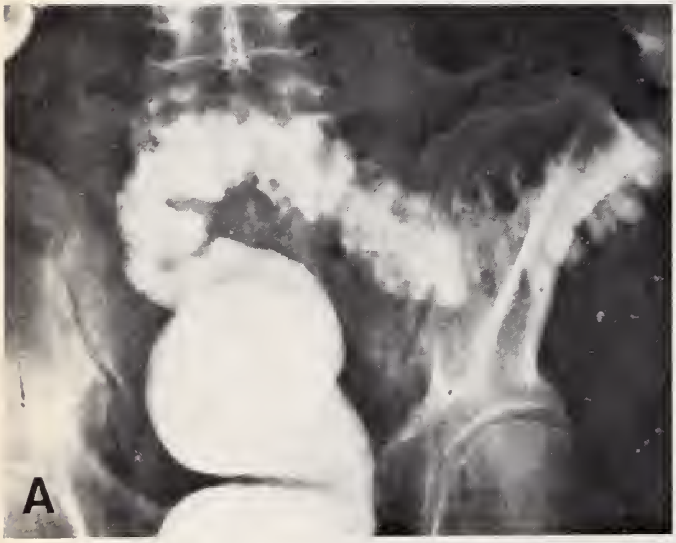


FIG. 21a. Diverticulosis. There are multiple diverticula in the sigmoid.

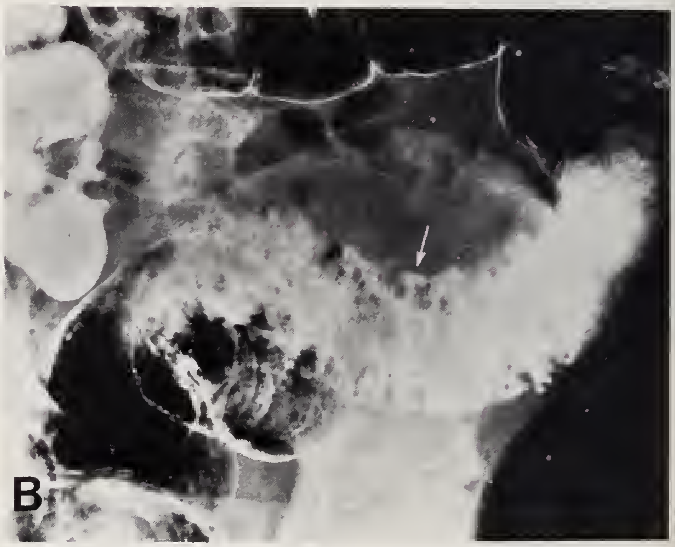


FIG. 21b. Same case as 21a, six months later. Numerous triangular projections are seen extending from the medial wall of the sigmoid. Normal diverticula are no longer present.

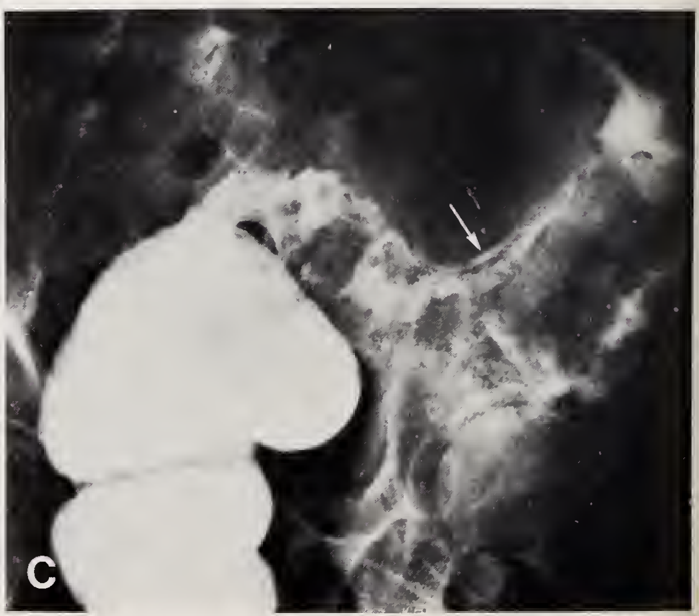


FIG. 21c. Same case as Fig. 21a and b, four months after 21b. A long paracolic fistulous tract is identified. This patient had diverticulosis for many years and then developed Crohn's disease of the sigmoid.

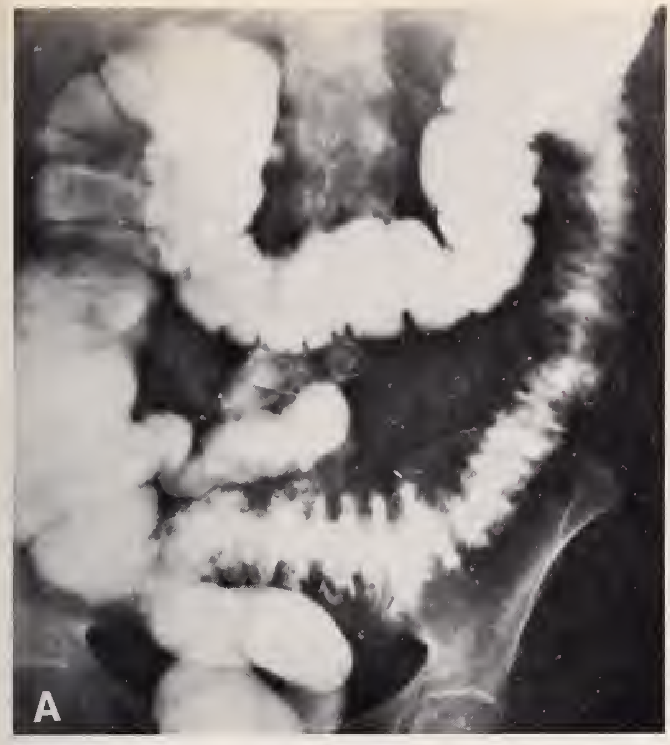


FIG. 22a. Diverticulosis. Numerous diverticula are seen involving the sigmoid and lower descending colon.

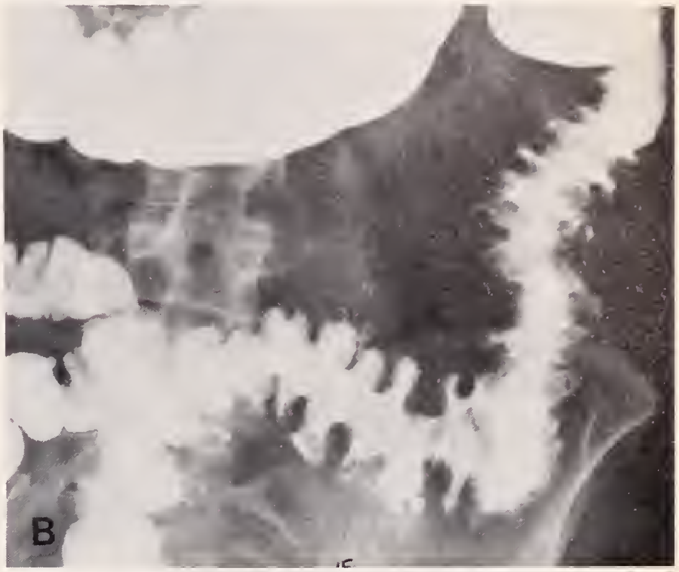


FIG. 22b. Same patient as Fig. 22a, six months later. The patient had developed severe diarrhea. There has been an alteration in the shape of the diverticula. These are now rectangular in configuration.

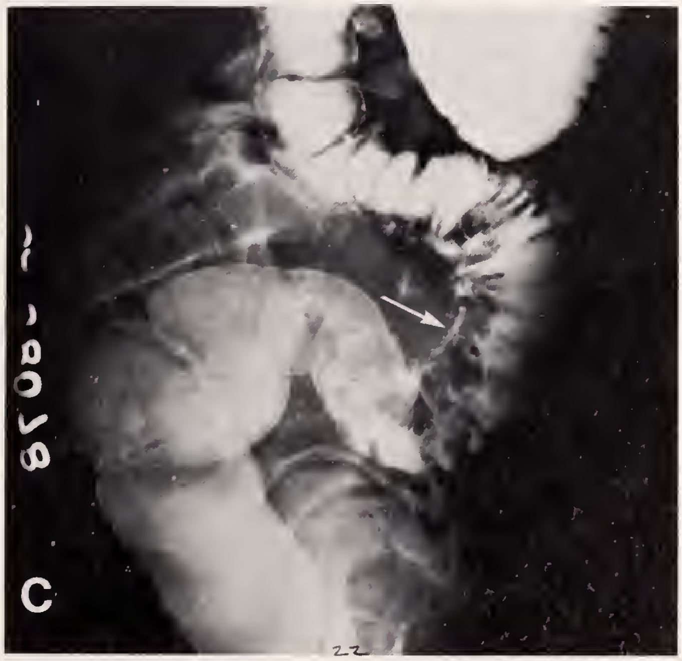


FIG. 22c. Same case as Fig. 22a and b, one year later. A long paracolic fistulous tract is now seen. Pathologic examination revealed Crohn's disease.

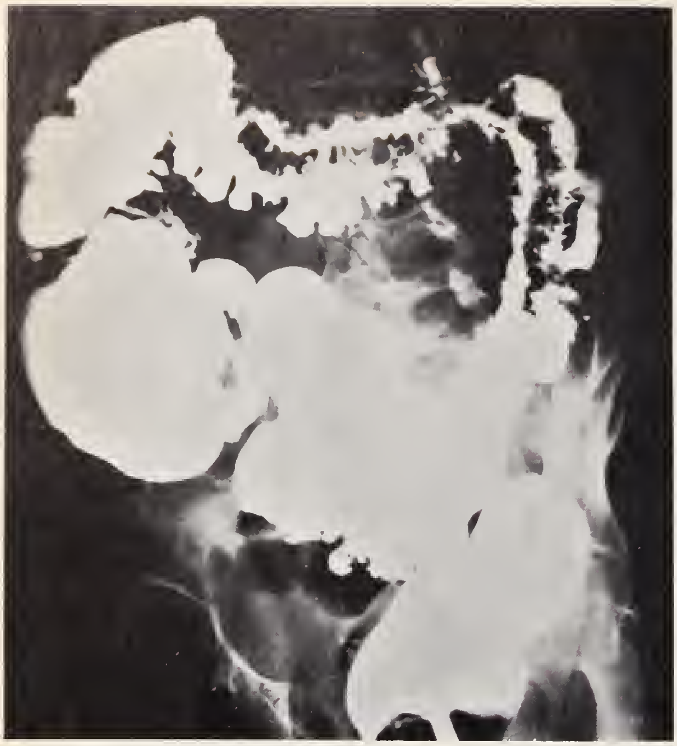


FIG. 23. Granulomatous colitis in association with a giant paracolic fistulous tract. A long fistulous tract involves the entire descending colon and the transverse colon. The tract parallels the mesentery. At autopsy, there was severe granulomatous colitis.

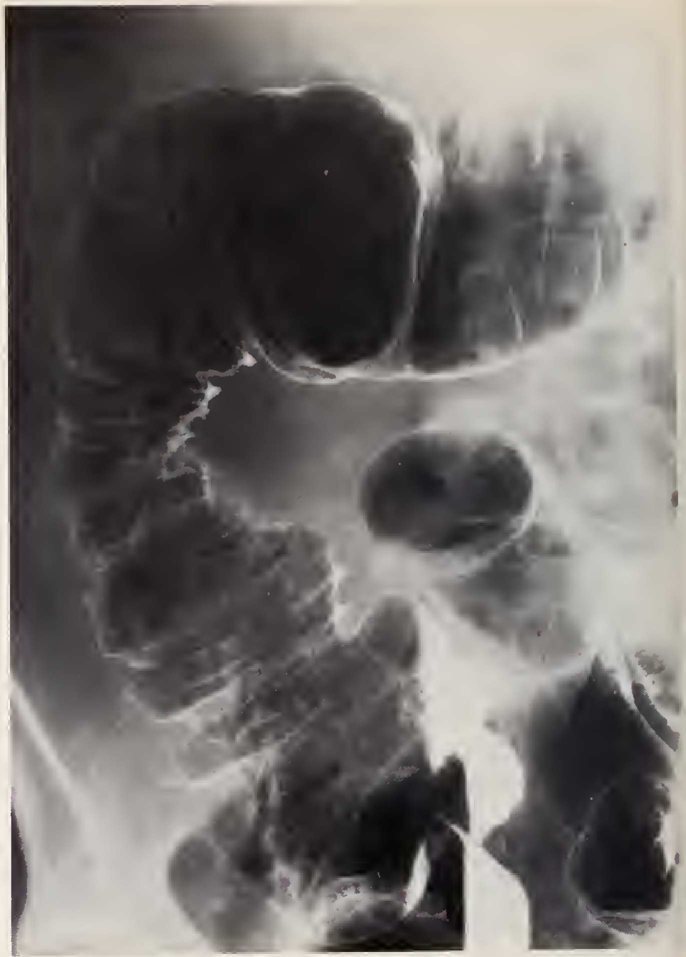


FIG. 24. Right sided diverticulitis. Air contrast study. There is a marked lack of distensibility of the medial border associated with rigidity, flattening and serrations of the contour. No filling defects are identified.

the course of the examination is helpful to reduce spasm and lessen discomfort to the patient.

We have not found it necessary to employ water soluble media in the examination of these patients. Free perforation should not occur during a carefully performed barium enema examination.

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Albumin Therapy For Brain Swelling In Cardiac Arrest: A Proposal

SYLVAN E. MOOLTEN, M.D.

Introduction

In these days of mobile resuscitation teams, the all too frequent delay in restoration of cardiac function in patients with cardiac arrest has created a population of decerebrate individuals in whom the only outlook is for severe dementia or persistent comatose, vegetative states. In a minority of cases, the patient, aided by intensive rehabilitation efforts, may regain some semblance of rational behavior and the capacity even to feed himself and walk. Even so, serious intellectual and personality deficits remain, often associated with aggressive behavior if not overt psychosis. In one case, a family won a tremendous sum in damages because the physician, while succeeding in getting the patient's heart to beat again, was unable to prevent the upper part of his brain from being destroyed so that, as a result, the man was left grossly impaired (1).

The after care of the patient with ischemic encephalopathy following cardiac arrest imposes a heavy physical burden on the medical and nursing staff of a hospital in preventing or treating bedsores and in maintaining nutrition through nasogastric tube feeding. This also incurs an intolerable financial burden on the family and community. Many of these "human vegetables" eventually die of aspiration pneumonia or urosepsis. One report describes a 20-year-old girl who had a cardiac arrest during a tonsillectomy. She died 7½ years later without having regained consciousness.

The need of the brain for oxygen and glucose is prodigious. One fifth or more of the total cardiac output goes to the brain, averaging about 800 cc per minute, from which the brain ordinarily extracts about 40 percent of the oxygen and 80 mg of glucose (2). Momentary interruption of blood flow to the brain, such as that which occurs for a few seconds in heart block, creates a serious oxygen and glucose deficit manifested clinically in abrupt loss of consciousness. When cerebral ischemia is less than one minute, the unconsciousness will last perhaps only a few minutes; whereas anoxia of three minutes or more may result in coma lasting several days.

The length of time that the brain will withstand complete ischemia without permanent damage has never been established with certainty. Even if the time could be determined, it would be found to depend upon such factors as age, the previous condition of the brain, and the body temperature. Thus at birth, and for about one month afterward, the brain is extremely resistant to anoxia of any form. With further development and, particularly with old age, the sensitivity of the brain to anoxia increases proportionately. At normal body temperature, the currently accepted standard time for cerebral ischemia with subsequent recovery is four minutes, although this figure was arrived at on a purely arbitrary basis (3). In all likelihood, it is probably nearer three minutes (4).

The degree of success of resuscitative procedures varies. In most patients successfully resuscitated without residual disorder of the nervous system, cardiac massage had been instituted shortly after cardiac arrest, that is, within the four-minute limit, maintained in some instances for long periods of time. For example, in eight of nine cases reported by Dupont et al, external cardiac massage was maintained for over 20 minutes, and in one case for 3-1/2 hours, with complete restoration of intellectual function (5). The poorest results have been noted in patients with cardiogenic shock, asystole or bradycardia following myocardial infarction, persistent hypotension after resuscitation, and recurrent arrest after myocardial infarction. On the other hand, cardiac arrest in an otherwise healthy person during a well controlled situation in the operating room and diagnosed within the first two or three minutes yields a high success rate. The presence of dilated fixed pupils is no longer regarded as indicating irreversible brain damage and numerous cases are now reported with complete recovery despite fixed dilated pupils for as long as 45 minutes (6).

The inference that the cells of the cerebral cortex are irreversibly damaged after periods of ischemia longer than four minutes is not necessarily valid in every case.

From the Department of Medical Education and Laboratory, Roosevelt Hospital, Metuchen, N.J. 08840.

Requests for reprints should be sent to Dr. Sylvan E. Moolten, Roosevelt Hospital, Box 151, Metuchen, N.J. 08840.

In the case described by Roe, a 23-year-old girl was resuscitated with complete recovery after a 20-minute-period during which there was no effective heart action (7).

"This patient had sustained an anterior blunt chest injury in an automobile accident. When the pericardium was opened she began to exsanguinate through a huge uncontrollable rent in her right atrial appendage. In desperation, electrical ventricular fibrillation was instituted but the large venous pool continued to pour through the vena cava. She was rapidly infused with refrigerated bank blood and given one or two ventricular squeezes from the surgeon's hand. However, quite clearly there was no effective circulation during the course of the 20-minute operation. When the repair was accomplished, she was given cardiac massage and within less than ten minutes, she had regained normal cardiac action. Within three to four hours she woke up and was completely lucid the next morning."

It cannot be doubted that the major factor in the favorable outcome in the above case was the persistence of a slight amount of blood flow after apparent cardiac standstill. The least trickle of blood can maintain the activity of nerve cells for a surprisingly long period, as first emphasized by Hill in 1900. Even stagnating blood about nerve cells prolongs their life span (8). Pike and his associates pointed out that slight fibrillation of the heart can maintain a small amount of blood flow even when one is unable to demonstrate function of the heart clinically except by direct inspection (9). This undoubtedly accounts for remarkable reports of recovery after hours of apparent death. A striking example of this possibility was reported by Schlachman et al in the case of a 69-year-old woman subjected to colostomy under high spinal anesthesia (10).

"As the abdomen was closed she went into shock. The blood pressure and pulse were unobtainable and no heart sounds could be heard. The patient was then considered clinically dead. She was given artificial respiration but was not given cardiac compression through the open chest until 1-1/2 hours later. During the intervening period the electrocardiogram revealed ventricular tachycardia with short runs of ventricular fibrillation. After the second manual compression of the heart sinus rhythm was established and cardiac contractions became normal. The patient made a complete recovery without neurologic sequelae."

The Role of Brain Swelling (Cerebral Edema)

Obviously anoxia cannot be considered the only factor or, in some instances, even the major factor. A large group of physiologic mechanisms acting singly or en masse are concerned. Among these, chief interests centers on brain swelling. When the circulation to the brain is reduced, its water-binding capacity increases to a remarkable degree because of the accumulation of sodium in the cytoplasm of the glial cells along with acid products of metabolism. These changes occur promptly at the moment of death. Alexander and Looney found that blocks of normal brain tissue, taken after death and immersed in saline solution ranging from 0.3 to 1.2 percent concentration, swell promptly and continue to swell up to eight days (11). Swelling failed to occur when brain tissue was immersed in 1.8 percent sodium chloride solution which is approximately twice the physiologic level. In some cases, the brain swelled even in ten percent sodium chloride solution! Stewart-Wallace cited data on the sodium content of the brain in cerebral edema compared with the normal brain (12). Edematous brain tissue was found to contain 58.9 mEq of sodium per 100 gm of dry tissue compared with a sodium content of 27 mEq in nonedematous tissue. The potassium levels were essentially unchanged. Chloride followed sodium, rising from 7.6 mEq in nonedematous brain tissue to 29.6 mEq in edematous brain.

The terms "brain swelling" and "cerebral edema" are now used interchangeably (13). According to Klatzo, cerebral edema can be classified into two major categories, vasogenic edema and cytotoxic edema (14). Vasogenic edema, characterized by increased permeability of the capillary epithelium of the brain, is noted in cases of brain tumor, abscesses, hemorrhage, infarction, trauma, lead encephalopathy, and purulent meningitis. Cytotoxic edema occurs in water intoxication, following cardiac arrest, or in asphyxia.

Distribution of cerebral edema varies with its cause. According to Bakay and Bendixen, the gray matter of the brain is much more susceptible to hypoxia than the white matter (15). The white matter generally is considered to be more susceptible in cases of various types of intoxication, hypertensive encephalopathy, cranial trauma, water intoxication, heat stroke, severe burns, and carbon dioxide retention with hypoxemia.

When brain swelling is caused by cerebral ischemia, that is, in cardiac arrest, all the elements of the brain (neurons, glia and endothelial cells) may undergo swelling with concomitant reduction of the extracellular-fluid space. These cells swell within seconds of hypoxia because of failure of the ATP-dependent sodium pump within the cells (13). Sodium accumulates rapidly within the cells and water follows to maintain osmotic equilibrium. At autopsy the characteristic finding is abnormal hydration of the fixed elements of brain tissue. In this respect, brain swelling (cerebral edema) differs sharply from the edema of other tissues (16).

Ordinarily, there is a reserve space within the cranial cavity filled with cerebrospinal fluid and blood. The reserve space, largely the subarachnoid space and cerebral ventricles, amounts to between four and nine percent of the total cranial capacity. Once the brain swells to the limit of this capacity, its further expansion occurs by downward movement through the foramen magnum into the spinal canal and by its crowding action on intracerebral capillaries and venules which shuts off the flow of blood by tamponade. The resulting drop in intracerebral blood flow causes additional brain damage and therefore additional swelling. A vicious cycle then arises in which ischemic injury→brain swelling→capillary tamponade→ischemic injury→brain swelling.

In the initial stages of anoxia autoregulation of the intracerebral circulation may compensate through vasodilation. Later, this protective mechanism is overwhelmed by the rise in intracranial pressure.

In short, the permanent damage to the brain produced by cardiac arrest is more the result of the secondary continuing ischemia caused by brain swelling than the initial anoxic insult. One might therefore predict that if brain swelling could be relieved quickly enough, the "safe limit" might be extended well beyond the four-minute allowable maximum between the onset of cardiac arrest and the onset of cardiac massage.

The picture of brain swelling at autopsy is well defined. The brain is swollen and fills the cavity of the skull completely so that the gyri are flattened against the overlying bone and the sulci are correspondingly narrowed. The cerebral ventricles are also reduced in size. Characteristically, the brain stem is jammed downward into the foramen magnum together with the posterior portion of the cerebellum to form a pressure cone. The uncus of each of the temporal lobes is also wedged downward through the tentorium. The superficial veins are thereby kinked and compressed so as to produce marked stasis in the smaller vessels and occasional brain stem hemorrhages. In severe cases, the arteries are compressed against bony and dural prominences to produce widespread acute ischemic necrosis of most or all of the brain (17).

Microscopically, the picture suggests edema because of the empty spaces about small blood vessels in the cortical gray matter. These vessels are narrowed or appear completely closed off by what seems to be a collar of fluid. Although the findings might suggest perivascular edema, electron microscopy reveals that the edema actually represents extreme swelling of the sucker feet of the astrocytes apposed to the outer wall of blood vessels (16, 18). In short, then, the picture is actually not that of edema in the ordinary sense but of intracellular imbibition of water by astrocytes. In addition to compression of blood vessels, swelling of the astrocytes might compress the nerve cells and fibers and thereby interfere with their normal function (19).

The Clinical Recognition of Brain Swelling

With the exception of neurosurgeons, to whom brain swelling is a familiar and disquieting complication of cranial trauma or surgery, the majority of clinicians are unaware of its existence and unprepared for its diagnosis. Clues to its presence in the conscious patient consist of unexplained headache, visual disturbances, vomiting, convulsive twitching, hemiparesis, paralysis of one or both sixth cranial nerves, or somnolence ending in stupor or coma. Papilledema is a valuable sign to the clinician accustomed to fundoscopy but it is not invariably present and may be inconspicuous. The cerebrospinal fluid may be under increased pressure but the cell count and protein content remain normal.

In the unconscious patient the clinical diagnosis of brain swelling must be based largely on suspicion aroused by the attendant circumstances. In the case of the patient with cardiac arrest, persistence of deep coma and failure to respond to painful stimulation shortly after successful cardiopulmonary resuscitation should constitute presumptive proof of brain swelling and the likelihood of irreversible brain damage if brain swelling is unrelieved.

Brain swelling (cerebral edema) of recognizable degree has been reported as the only finding of significance at postmortem, not only in the brain of patients dying in coma following successful cardiac resuscitation, but also in coma due to a variety of other causes (Table I).

TABLE I

Partial List of Conditions Associated with Brain Swelling

Craniocerebral trauma, including simple concussion
Irreversible hypoglycemic shock
Carbon monoxide poisoning
Heat stroke
Hypertensive encephalopathy
Lead poisoning
Adrenal insufficiency
Reye's syndrome
Alcoholism (alcoholic wet brain)
Respiratory failure in chronic obstructive pulmonary disease
Barbiturate poisoning
Acute laryngotracheobronchitis in young children
Mechanical strangulation
Impaired ventilation resulting from bulbar poliomyelitis or Guillain-Barré syndrome
Profound anemia as seen in pernicious anemia or severe iron deficiency anemia
Chronic hemorrhage
States of increased blood viscosity such as polycythemia vera
Vitamin A overdosage
Administration of tetracycline in predisposed children
Administration of tin salts in treatment of furunculosis
Water intoxication
Overhydration in treatment of diabetic coma

For example in one patient, a woman who had a cholecystectomy, nine liters of ordinary tap water were administered by a retention enema over a period of 30 hours, following which she developed convulsions and stupor with fatal outcome. Autopsy revealed massive brain swelling (20). In another case of water intoxication the patient developed irrational and agitated behavior with projectile vomiting following selfadministration of large quantities of hot water, orally, and tap water, rectally, in order to induce defecation (21). Brain swelling is well known as a complication of overhydration in treatment of diabetic coma (22) and may occur as a complication of dialysis for renal insufficiency, especially hemodialysis when insufficient consideration is given to maintain osmotic equilibrium.

Alcoholism may be the cause in some cases; when a patient develops the picture of "alcoholic wet brain" with headache, convulsions and stupor it may be mistaken for delirium tremens.

Brain swelling has been described in women taking contraceptive pills. It may occur in Addison's disease because of hyponatremia and hypotension, and also in patients under treatment with steroids when the steroid dose is lowered rapidly or withdrawn (23).

Prophylaxis Of Brain Swelling In Cardiac Arrest

When cardiac arrest occurs in the operating room, it is commonly incumbent upon the anesthesiologist to conduct the immediate and subsequent management of the case. Anesthesiologists are well versed not only in resuscitative procedures but also in the management of the problems that follow, specifically ischemic brain damage. They commonly employ controlled hypothermia, limitation of fluid intake, and administration of osmotic diuretics (24).

The problem is much more complicated when cardiac arrest occurs in myocardial infarction, particularly with cardiogenic shock. Confronted with a patient in a state of shock following resuscitation, the clinician's first impulse might be to give fluid intravenously, usually five percent glucose in distilled water or similar electrolyte-poor solutions. Prophylaxis of brain swelling requires that such treatment be avoided. The clinician's reluctance to give saline or sodium lactate in such instances is understandable when he is aware of the potential hazard of brain swelling, a condition that is still widely regarded as essentially the same as edema occurring in other tissues. Experimental and clinical studies have made it abundantly clear that electrolyte-poor fluids actually predispose to brain swelling whereas fluids containing sodium ion, such as normal saline, present less of a hazard, and solutions containing higher concentrations of sodium chloride will, if anything, reduce brain swelling, although temporarily. Neurosurgeons are familiar with this problem and have learned to circumvent brain swelling during and after craniotomy by employing intravenous solutions of 2.5 percent glucose in 0.42 percent sodium chloride (25).

Nevertheless prophylaxis of brain swelling requires treatment of shock in myocardial infarction by use of plasma expanders. Low molecular weight dextran has been advocated in such cases as an antisludging agent that, by reducing blood viscosity, improves peripheral blood flow and releases sequestered blood cells (26). The cardiac output also increases subsequent to an increase in venous return to the heart. Solutions of albumin have been recommended for the same purpose (27). Indeed, albumin solutions in a concentration of 3.0 to 3.5 gm percent in isotonic saline are more effective per volume added than any other known fluid in decreasing blood viscosity (28).

Active Treatment of Brain Swelling

Treatment with Hypertonic Solutions: Treatment of brain swelling by means of osmotically active agents was encouraged by the experiments of Weed and McKibben in 1919 who tested hypertonic solutions of sodium chloride, sodium sulfate, sodium bicarbonate, and dextrose in cats (29). However, the employment of this class of substances in treating brain swelling in humans has generally gone into discard, not only because of their transient action but also because of certain harmful potentials. Among the latter is a rebound effect with all these agents, that may actually aggravate the degree of swelling after temporary improvement (30).

For example, glucose in 50 percent concentration is rapidly metabolized and, when taken up into the cells in the brain, increases the avidity of the brain cells for water. Less rebound occurred with sucrose than with glucose, but this sugar is nephrotoxic and produces considerable diuresis. In dogs, the rebound following a 30 percent solution of sodium chloride amounted to a rise of more than twice the initial pressure (31). Hypertonic sodium chloride given intravenously may induce subdural or intracranial hemorrhage, possibly because of rapid shrinkage of the brain which may tear bridging veins (32).

Intravenous Urea: Intravenous infusion of urea is usually given as a 30 percent solution in five or ten percent dextrose or ten percent invert sugar in water. Urea is a highly effective diuretic after an initial phase of hemodilution. It is said to produce the greatest amount of dehydration with the least amount of change in electrolytes. This agent has won much popularity among neurosurgeons since it has the ability to cause rapid shrinkage of the brain. Several authors have cautioned against its use because of the rebound swelling that may also occur when its dehydrating effect wears off, thereby increasing the volume of brain tissue even more (33–35). Urea has also been reported to cause subdural hematoma and to increase the risk of venous thrombosis (36). It may produce hemoglobinuria when given simultaneously with hypothermia.

Mannitol: Using mannitol intravenously in relieving brain swelling has been common practice for some years. It produces transient hemodilution followed by prompt diuresis. Mannitol is given usually in dosages of 1.5 to 2.0 gm per kg of body weight in 15 to 25 percent solution over a period of 30 to 60 minutes. Although its osmotic activity is one-third that of urea, it remains extracellular; this has been said to account for reports that the rebound of intracranial pressure is less with mannitol than with urea. Its side effects result largely from fluid and electrolyte imbalance. In a patient with impaired renal function and inadequate urine flow, large doses may precipitate pulmonary edema, water intoxication, and fulminating congestive heart failure–especially in patients with diminished cardiac reserve.

Glycerol: Glycerol, given by mouth in a dose of 1 to 5 gm per kg of body weight, has been reported to decrease cerebrospinal fluid pressure without rebound and without disturbance in electrolyte balance (37). It has been shown, however, to elevate serum glucose to dangerously high levels in predisposed patients and, in some cases, to precipitate hyperosmolar nonketotic coma (38). Its action in lowering intracranial pressure is shortlived and frequent administration has been found to result in a rebound increase in intracranial tension and clinical deterioration (39).

Steroids: In recent years large doses of corticosteroids have been employed in treatment of brain swelling. Theoretically, corticosteroids preserve the membranes of intracellular lysosomes and thereby reduce the tendency to autolysis of brain tissue during periods of relative ischemia. According to Katzman and Leiderman, cortisone tends to restore ionic equilibrium in the brain cells by favoring the uptake and retention of potassium (40).

Dexamethasone has been shown to reduce the focal and general signs of brain tumor dramatically and rapidly, especially in the case of metastatic tumors responsible for severe vasogenic edema of the brain. However there are no data, clinical or experimental, to indicate a beneficial effect of dexamethasone or other glucocorticoids in the cytotoxic edema of hypoosmolality, asphyxia or hypoxia. Accordingly there is little basis for recommending their use in the treatment of the common cytotoxic edemas such as cerebral edema associated with cardiac arrest (13).

Hypothermia: Hypothermia, although shown experimentally to protect against brain swelling, is attended with difficulties when applied to the human patient. The optimum range of hypothermia to reduce brain swelling is considered to lie between 28 and 30 degrees C. Hypothermia carries few risks if carried out correctly but may produce ventricular fibrillation if the body temperature drops below 28 degrees C. Other side effects include acidosis and hypotension. Careful monitoring is required and much time is lost before adequate hypothermia is established. The results are unpredictable and supplementary use of hypertonic solutions may be required (41).

The technique of selective brain cooling by perfusion techniques, as described in the dog and in one human patient by White and his associates is still in an experimental stage (42).

Treatment with Macromolecular Solutes: Regardless of concern over brain swelling as such, one must not lose sight of the fact that the primary aim in treatment is to restore adequate circulation to the brain. Granted that brain swelling constitutes the major obstacle to free flow of blood, it would be short-sighted to rely wholly on dehydrating agents without concomitant reduction in blood viscosity.

Whole blood viscosity increases steeply with the hematocrit throughout the accepted normal range and not just when it exceeds 0.50, as is commonly believed. As shown by Thomas and his associates patients with a hematocrit over 0.46, whatever the cause, may have impaired cerebral blood flow (43). Older patients in particular appear less able to maintain cerebral blood flow in the presence of higher viscosity. Of still greater importance is the local effect on viscosity produced by cell aggregation (blood sludging) as a result of hypoxia and metabolic acidosis (44).

Reduction of blood viscosity must be given major consideration in preventing permanent neurological deficit following cardiac arrest. In the first place when brain swelling develops, the shift of ions and water from blood plasma to perivascular astrocytes not only narrows the lumen of brain capillaries and venules but also increases the viscosity of the blood contained in these vessels and favors aggregation of its red blood cells (blood sludging).

Of equal if not greater importance is the general increase in blood viscosity that occurs in cardiac arrest caused by dehydration induced by excessive sweating, vomiting or diarrhea, and the dehydrating action of osmotic diuretics. Herein perhaps lies one of the chief indictments against the use of urea or mannitol.

Plasma osmolality rises even more, in many cases to levels regarded as potentially lethal, as a result of the injection of hypertonic sodium bicarbonate (7.5 percent) as part of the resuscitation procedure following cardiac arrest (45). The rise in blood viscosity is further augmented by the increased level of blood fibrinogen that occurs in patients with myocardial infarction as well as in patients with simple angina pectoris (46, 47).

The problem of blood rheology is particularly relevant to brain swelling, a condition in which a finite pressure is required to overcome the tendency of red blood cells to become aggregated. As stated by Merrill, "One can visualize this qualitatively by thinking what would happen if the grains of sand moving down the throat of an hourglass (3 minute egg timer) were slightly sticky toward each other. After a particular precapillary sphincter has closed off a flow the restarting of a flow necessitates the disintegration of the temporary red cell network, the cohesiveness of which is proportional to the yield stress" (28).

From theoretical considerations, the ideal hypertonic solution for reducing intracranial pressure is one that not only has a high osmotic pressure but contains solutes that will remain in the blood vessels after injection to exert a continued osmotic effect and at the same time reduce blood viscosity.

The normal relative impermeability of the blood capillaries in man to serum proteins has suggested the use of a hyperosmotic solution of blood serum (48). However, the use of concentrated serum or plasma never gained wide acceptance, probably because of observations of undesirable side effects caused by the presence of isoagglutinins for the recipient's red cells, fibrin masses, and the ever-present hazard of serum hepatitis.

The logical substitute was normal human serum albumin. When administered intravenously in concentrated form, albumin causes a shift of fluid from the interstitial spaces into the circulation. In a normally hydrated person, each volume of 25 percent albumin solution draws about 3.5 volumes of additional fluid into the circulation within 15 minutes. It is an ideal agent for restoring blood volume, 25 gm in 100 ml solution being equivalent to a transfusion of approximately 500 ml of fluid. Its smaller molecular weight (66,000) and greater net charge render it far more effective than globulin in maintaining the colloid osmotic pressure of the plasma (49). In further contrast to the high molecular-weight globulin fractions of plasma and plasma fibrinogen, albumin inhibits red cell aggregation and entrapment within the vessels of the microvasculature and indeed, as mentioned above, is more effective per volume added than any other known fluid in decreasing blood viscosity by dilution (28, 50). These qualities of albumin are of surpassing importance in the case of brain swelling, in which inspissation of blood and sludging of blood cells in the microvasculature constitute the major impediment to restoration of blood flow (51).

Albumin in its present form first became available in response to an urgent request from the Armed Forces during World War II for a safe blood substitute for use in traumatic shock (52). Low molecular weight dextran, polyvinyl pyrrolidine and gelatin also proved effective in the emergency treatment of shock and have also been considered for application in treatment of brain swelling. However their excessive viscosity in higher concentrations tends to cause sludging of blood cells as well as other undesirable side effects. Concentrated albumin, unlike concentrated plasma or gelatin, is only as viscous as whole blood with a hematocrit reading of 50 percent. The rapid lowering of blood viscosity that follows administration of albumin makes it therefore uniquely suited to the treatment of conditions in which blood perfusion is impaired. The same quality probably accounts for the fact that albumin appears to be more readily tolerated by patients with mild congestive failure than whole blood or other more viscous colloidal solutions (53).

The chemical properties of salt-poor albumin (the 25% solution contains 8 mEq of sodium per 50 ml) as prepared from human blood plasma make possible its storage in a stable concentrated solution free of any preservative with potential injurious effects. Because it is heated for ten hours at 60 degrees C without deterioration, it is freed of infective agents including the virus of serum hepatitis. Albumin solutions rarely give rise to any immediate reactions other than occasional pyrogenic reactions or those that result from increase of plasma volume. One important disadvantage of albumin is its cost, which argues against its indiscriminate employment in situations of lesser risk to life or health.

In giving albumin, one must consider the possible risk of increasing blood volume rapidly in patients with diminished cardiac reserve who may thereby become acutely decompensated. The risk is particularly high in the case of patients resuscitated from cardiac arrest caused by myocardial infarction. The clinician is thereby confronted with a therapeutic dilemma in which the risk of pulmonary edema must be weighed against the threat of irreversible brain damage. If pulmonary edema supervenes, one can resort to oxygen under positive pressure, phlebotomy, and diuretics. Obviously such a patient must be carefully monitored.

Even so, as already mentioned, albumin has been advocated as a means of reducing blood viscosity in cardiogenic shock and thus increasing coronary flow (27). Indeed, an initial trial of fluid loading to improve cardiac performance is accepted by many investigators as a rational early approach to patients with the shock syndrome in myocardial infarction who exhibit normal or reduced central venous pressure (54–57).

Evidence for the effectiveness of serum albumin therapy in reducing cerebral edema was reported in 1944 by Sheldon, Pudenz and Craig at the National Naval Medical Center in connection with cases of head injury and, in 1948, by Gates and Craig at the Mayo Clinic in connection with both head injury and postoperative management of intracranial tumor (58, 59). In a series of 20 cases in which the results could be evaluated, definite improvement occurred in eight of the cases immediately after administration of serum albumin and delayed improvement in four. No benefit was observed in the remaining eight cases. There was no indication of untoward reaction in any of the cases. The albumin was administered in a single dose, the best results being obtained with a dose of 60 to 80 cc of the 25 percent solution given in a period of eight to ten minutes. Patients were not permitted to take any fluids for the next eight hours.

In the following year Seldon and his associates of the Section of Anesthesiology of the Mayo Clinic reported their experiences in two cases of postanesthetic anoxia (60). The first was that of a 27-year-old woman who failed to recover from prolonged anesthesia given during mastectomy. She remained comatose and exhibited constant purposeless movements of the arms and legs. The pupils were dilated, corneal reflexes absent and Babinski reflexes present bilaterally. She had three episodes of convulsion. She was given three doses of 25 percent human serum albumin intravenously in amounts of 100 ml each during a period of 12 hours and had rapid improvement with uneventful recovery. She had completely normal neurologic findings 21 days postoperatively.

The second case was that of a 50-year-old man with carcinoma of the base of the tongue who developed laryngospasm with complete anoxia for a period of eight minutes during an attempt at general anesthesia by intravenous pentothal sodium. Following tracheotomy and resuscitation he remained motionless and had bilateral Babinski reflex and marked ankle clonus; then he began to move his extremities in such a purposeless manner it was necessary to apply physical restraint. Five hours after restoration of respiration he was in coma with some evidence of spasticity. Albumin was given intravenously in three doses of 25 gm each (25 percent solution) during a period of about 7-½ hours. Definite improvement was observed five minutes after the first injection and well before the time of the third injection, after which he was alert and fully oriented and cooperative.

On the supposition that cerebral edema is probably responsible for the severe complications seen often in barbiturate poisoning, Mousel formulated a plan of treatment with 25 percent human serum albumin (61). Three patients were reported to be successfully treated by this means after analeptics had failed to improve their condition. To what extent serum albumin as such was responsible for recovery is not entirely certain in these cases because of the long periods elapsing between its administration and the return of deep reflexes and other signs of improvement, ranging from eight to 23 hours. The occurrence of brain swelling in barbiturate poisoning may reflect the hypoxic effect of impaired respiration caused by the barbiturates.

Albumin was found effective by Post et al in patients with hepatic coma, perhaps because of its effect in overcoming brain swelling (62). Of 16 patients in coma or semicoma, nine recovered from the coma. Warthin reported improvement in four of eight patients with hepatic coma given albumin intravenously (63).

A more convincing case for serum albumin may be made for its use in carbon monoxide poisoning. As demonstrated by Forbes, Cobb and Fremont-Smith (1924), fatal exposure to carbon monoxide is associated with extreme brain swelling with variable stasis or collapse of cerebral blood vessels (64). They reported success in relieving the experimental cerebral edema in animals and the headache in human beings suffering from carbon monoxide poisoning by the use of intravenous hypertonic saline. In the light of newer knowledge it might be appropriate to employ intravenous albumin in preference to saline in such cases.

In 1951, Cole described the use of albumin in a case of cardiac arrest occurring in a 21-year-old man following induction of spinal anesthesia (65). Cardiac massage was started within five minutes and heartbeat returned after a total of 11 minutes. Cerebral edema was diagnosed on the basis of the events that followed restoration of cardiac function. The patient was in coma and had generalized spasm, rigidity and convulsions. Pulmonary edema was also present and treated with oxygen under pressure. Five hours after cardiac resuscitation, albumin was given 25 mg intravenously and one half hour later the patient opened his eyes, appeared to swallow, and moved for the first time. He was given an additional dose one hour later and that evening he extended a hand to his friend, rose to his knees, and on the following day was able to make sounds but did not speak. Another dose was given intravenously and on the third day he was able to stand and walk with assistance. From then on he improved except for occasional hallucinations and periods of irrationality. Recovery was complete within three weeks.

The use of albumin accompanied by Novaldin, an analgesic antipyretic drug, was reported by Sikes to bring about dramatic improvement in a short time in psychiatric patients treated with insulin in whom hypoglycemic coma threatened to be irreversible (66). Similar results were reported by Jameson and Ford (67). They reported that Novaldin alone or albumin alone was not particularly effective. The dose of albumin in these cases was rather small, amounting to a single injection of 5 gm in 25 percent solution.

In spite of these favorable accounts of albumin therapy, its use has gained little headway as a general treatment of brain swelling, possibly because of the lack of carefully designed clinical and experimental studies comparing the results in cytotoxic brain swelling caused by anoxia with those in vasogenic brain swelling. One might question the applicability to anoxic encephalopathy from reports of negative conclusions about albumin therapy drawn from experiences with the vasogenic form of brain swelling encountered, for example, in patients with brain tumor (68). Bakay and Sweet gave six patients 25 gm of albumin in 100 ml of solution, and found almost no change in the intracranial pressure (69). Clasen et al reported negative results with albumin in dogs with experimental vasogenic edema of the brain produced by freezing the brain through the intact skull (70).

Case Reports

My own interest in the subject was aroused nearly 25 years ago when I was called into consultation in the case of a boy of 11 who had strangled himself.

When brought to the hospital, the patient seemed at the point of death and was rigid and unconscious. His pulse was feeble and rapid (180) and his respirations were rapid and gasping, rising to 60 per minute, and occasionally periodic. A ring of reddened skin encircled his neck. The story was elicited that he had been found by his parents in an upstairs bathroom kneeling on the floor with a tight noose about his neck, having strangled himself either accidentally at play or with suicidal intent.

On the morning after admission to the hospital he was still alive but had irregular periodic breathing. His pupils responded slightly to light and he moved his limbs occasionally on stimulation. A positive Babinski sign was present bilaterally. The picture suggested edema of the brain because of the persistent coma, pupillary changes and abnormal breathing.

Intravenous injection of 50 cc of 50 percent glucose gave transient slight improvement. Later the same day his condition underwent rapid deterioration. His coma grew deeper and his pupils became dilated and fixed to light. At 7 p.m. I suggested intravenous injection of one unit of albumin (12.5 gm in 25 percent solution). Soon after the injection there was dramatic improvement and on the next morning he was conscious and able to swallow food but had occasional torsion spasms. Lumbar puncture showed normal pressure of cerebrospinal fluid.

Thereafter he recovered rapidly and was allowed to return home on the 18th day. On a return visit one month later he remembered the nurses and children with whom he had played in the hospital but had complete amnesia about the strangulation episode. Five months later on a return visit he walked with slightly outspread legs like a "punch drunk" pugilist, but was quite clear mentally. He had returned to school and had shown only slight reduction in mentation.

The results of albumin in the above case were so impressive that I made it my primary recommendation in other cases of suspected brain swelling. For example, albumin was given four days after admission to a 44-year-old man in coma with decerebrate posture and sixth nerve paralysis following severe skull injury. Following the injection he showed steady improvement but continued to show signs of slight diffuse frontal lobe impairment in the form of euphoria, juvenility and short attention span.

A third case also deserves mention. This was the case of an 11-year-old girl who fell in the street striking her head, whereupon she developed severe headache, vomited and went into coma. Examination 12 hours later showed persistent coma with left hemiparesis. Bilateral trephines were performed 24 hours after the injury in an effort to locate a subdural hematoma but none was found. Following this her coma deepened. I recommended albumin intravenously but this was countermanded by the neurosurgeon in attendance. However, on his departure for the weekend the family physician gave intravenous albumin. Less than one hour after the needle was inserted into her vein she was wide awake, sitting up in bed and asked to go home. She remained well thereafter.

In two other cases, intravenous albumin gave temporary benefit. In one case the patient had malignant hypertension and developed a drop in blood pressure from 260/180 to 75/50 following thoracolumbar sympathectomy. The sudden precipitous fall in blood pressure caused deep coma. Brain swelling was suspected and albumin was given intravenously. The injection led to return of consciousness and other cerebral functions but the patient died ten weeks later of pneumonia.

In another case, that of a man with glomerulonephritis and hypertensive encephalopathy, transient improvement resulted from intravenous albumin but he died eventually of uremia. In one case of deep barbiturate coma albumin was ineffective.

A few months ago another case came to my attention, that of a 91-year-old woman admitted to Roosevelt Hospital July 1, 1976, because of hypertension, vertigo and repeated falls. Shortly after admission her blood pressure had risen to 250/130. She had slight edema of the feet. She was treated with Aldomet 240 mg every six hours and Esidrix 50 mg, four times a day. On the morning of her third day in the hospital her blood pressure had dropped to 116/70, and at 4:30 p.m. had dropped to 84/48. Her pulse had slowed to 34. She was transferred to the Intensive Care Unit and given an intravenous infusion of five percent dextrose in distilled water. Following this her blood pressure rose to 154/80 and her pulse to 50. She was slightly lethargic. On the following day her blood pressure was 195/90. She was treated once again with Aldomet and Esidrix. Three days later she became very lethargic and went into coma. Her pupils were contracted but equal and reacted to light. The fundi could not be visualized. There was no nystagmus. The heart rate was 56. Her blood pressure was 90/50 but later rose to 112/60.

The patient was thought to be suffering from cerebral ischemia as a result of the sharp drop in blood pressure and as a result had developed acute brain swelling. She was therefore given a single unit of albumin intravenously. On the following day she was much improved. She was alert and able to follow instructions. Her blood pressure was 134/70. She moved all her extremities freely. Later the same day her blood pressure rose to 210/100. She was confused but had no complaints. From then on she showed consistent improvement. She spoke well and was able to walk. Her mentality seemed slightly dull and she had some difficulty with memory.

In this last case the patient's brain swelling was believed to result primarily from the precipitous drop in blood pressure aggravated by the administration of five percent glucose in distilled water intravenously. As already mentioned, the brain is normally hypertonic with respect to the blood and the injured brain has an even greater avidity for water when given without adequate electrolytes.

Conclusions

On the basis of the results reported in the literature and the writer's own experience with albumin, this agent is proposed as the ideal agent for the treatment of brain swelling following successful resuscitation in cases of cardiac arrest for the following reasons:

1. Its action in reducing brain swelling is nearly as rapid as that of such osmotic diuretics as urea or mannitol.
2. There is no evidence of a rebound effect such as may occur with osmotic diuretics or glycerol.
3. It reduces blood viscosity and thereby improves the perfusion of blood through the ischemic brain in sharp contrast to the effects of osmotic diuretics, which, by increasing blood viscosity through rapid diuresis, favor aggregation of red blood cells in the cerebral microvasculature (blood sludging).
4. Albumin given in concentrated form increases blood volume and thereby overcomes the circulatory impairment caused by shock or dehydration.
5. The administration of albumin requires minimal effort on the part of hospital personnel in contrast to artificial hypothermia, which is much slower in action and uncertain in its effects, and requires a well-trained team and careful monitoring.
6. A single dose of 25 gm may be effective although in many cases it may be necessary to repeat the dose two or three times at intervals of four to six hours.
7. Its use in the case of patients with myocardial infarction must be carefully monitored because of the potential hazard of volume overload. To some extent this danger is outweighed by its favorable action against cardiogenic shock in patients who exhibit normal or reduced central venous pressure.
8. Albumin's use is almost entirely free of other hazards, in which respect it is superior to glycerol or steroids.

Summary

The major threat to the brain following cardiac arrest is not so much the initial ischemia as the secondary brain swelling that follows, causing the brain to expand to the limits of the cranium and impairing cerebral blood flow by tamponade of small blood vessels. To prevent irreversible brain damage it is necessary not only to relieve intracerebral edema, which is largely intracellular, but to restore blood perfusion against the resistance offered by sludged blood cells in the narrowed cerebral blood vessels. To achieve these goals, prompt intravenous administration of concentrated human serum albumin is proposed as the treatment of choice. This agent is uniquely suited to this purpose because of its effectiveness not only in drawing water from the brain but, more importantly, in reducing blood viscosity. There is reasonable justification for the premise that prompt administration of albumin in patients resuscitated after cardiac arrest may minimize or prevent irreversible brain damage even though the period of cerebral anoxia is longer than the currently accepted safe interval of four minutes.

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Serologic Tests for Syphilis: A Guide to Interpretation in Various Stages of Disease

LUIS BRACERO, M.D., GARY P. WORMSER, M.D., AND EDWARD J. BOTTONE, Ph.D.

The diagnosis and staging of syphilis require an integration of historical data, physical findings, darkfield examination, and serologic tests. In many instances, diagnosis is based solely on this last parameter. Hence, it is imperative that the physician have a thorough understanding of the sensitivity (ability to detect presence of disease), specificity (ability to be nonreactive in absence of disease), and indications for the various treponemal and nontreponemal tests that are available to him.

Invasion of the human host with *Treponema pallidum* results in the production of two types of antibodies. The first, which is nonspecific and known as reaginic antibody, reacts with a nontreponemal cardiolipin-lecithin-cholesterol antigen. This antibody belongs to the IgG and IgM classes of immunoglobulins and can be detected through the use of flocculation [venereal disease research laboratory (VDRL), rapid plasma reagin (RPR), automated reagin test (ART)] or complement fixation (Kolmer, Wasserman) tests. The second antibody is specific, reacts with treponemal antigen, and can be assayed for by indirect fluorescence (FTA), microhemagglutination (MHA-TP) and immobilization (TPI) tests.

Syphilis serology is probably the diagnostic and staging criterion causing the most confusion among physicians. This problem is further complicated as interpretation and significance vary according to whether serum or cerebrospinal fluid is tested.

The aim of this communication is to present a compilation of the presently utilized serologic tests for syphilis with their percentages of reactivity in the various stages of syphilis and in nonsyphilitics. Such an endeavor should aid the clinician in the proper interpretation of syphilis serology as a diagnostic adjunct.

Discussion

Table I shows the percentage of positive and negative reactions for the most widely used nontreponemal antibody test (VDRL) and the three treponemal antibody tests (FTA-Abs, MHA-TP, and the TPI) in the various stages of syphilis and in nonsyphilitics. Table II lists recommendations regarding the laboratory procedures most pertinent to the diagnosis of the various stages of disease.

Although the Tables are generally self-explanatory, several points are worth emphasizing. There is a multiplicity of nontreponemal antibody tests (VDRL, RPR, Kolmer, etc.) that use different methodologies to detect the same antibody and are thus interchangeable (17). The VDRL, which may be considered representative, is simple to perform, reproducible, and quantitative. Yet, there are important limitations to its use. Although a negative VDRL, in the absence of the prozone phenomenon, will effectively rule out secondary syphilis, a negative test will not exclude either primary or late syphilis (10, 11). Furthermore it is to be emphasized, that a false-positive serum VDRL is so frequent, that this test should never be the sole serological confirmatory study (11). In cerebrospinal fluid (CSF), the situation is reversed. Here, a false-positive VDRL is extremely rare and is thought to occur when serum positive for VDRL contaminates cerebrospinal fluid as by traumatic lumbar puncture or subarachnoid hemorrhage (21). A negative cerebrospinal fluid VDRL in patients with clinical neurosyphilis is, however, not uncommon (4, 5, 21).

The VDRL is easily quantitated and changes in titer provide additional useful diagnostic data. For example, the serum of infants born to mothers with a reactive serum VDRL may, in the absence of infection, also be reactive as a result of passive transplacental transfer of the maternal antibody. The VDRL from such an uninfected neonate will demonstrate a falling titer on serial examination whereas the titer of an infected, but untreated child, will remain stationary or rise (11, 20, 22). Quantitation of the VDRL also affords diagnostic infor-

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From the Section of Infectious Diseases, Veterans Administration Hospital, Bronx, N.Y. 10468 and the Department of Microbiology, The Mount Sinai Hospital and Mount Sinai School of Medicine of The City University of New York, New York, N.Y. 10029.

Requests for reprints should be sent to Gary P. Wormser, M. D., VA Medical Center, 130 W. Kingsbridge Road, Bronx, N.Y. 10468.

TABLE I

Comparative Results of Serologic Tests for Syphilis in Various Stages of Disease and in Nonsyphilitics (1–6)

	Stages of Disease					Nonsyphilitics
Test (serum)	Neonatal Congenital	Primary	Secondary	Late latent late benign cardiovascular neurosyphilis	Neurosyphilis Cerebrospinal fluid serology	False-positive serum***
VDRL	Must be differentiated from maternal VDRL. Only a rising titer diagnostic	70%	99%	70%	22–61%	Frequent occurrence, eg. may complicate many acute and chronic infectious diseases, pregnancy, collagen disease, and narcotic addiction (10, 11).
FTA-ABS	Must be differentiated from maternal FTA-Abs*	85%	99%	98%	Variable**	0.5-1% in normals; false positive and borderline reactions occur more frequently with sera containing abnormal globulins, particularly antinuclear factors (≅ 10%) (11, 16–18).
MHA-TP	Insufficient Data	65%	96%	95%	Insufficient Data	Less than 1.5% in normals reported by most studies, but some studies have found a higher rate of false positivity (9%), particularly with sera demonstrating false-positive VDRL (3, 12–15)
TPI	Insufficient Data	50–60%	95%	95%	Insufficient Data	Rare but may occur if serum contains an antimicrobial active against *T. pallidum* (11).

* The FTA-Abs-IgM has been used to distinguish fetal from maternal treponemal antibody. However, the technique is not well standardized. 10% false positives (in part may be due to nontreponemal fetal IgM directed against maternal IgG) and 35% false negatives reported, particularly in cases acquired late in pregnancy (7–9)

** The specificity and sensitivity is not well established because of inadequate numbers of control and syphilitic CSF tested. The FTA appears to be more sensitive than the FTA-Abs which in turn is more sensitive than the FTA-IgM test (5, 6).

*** False-positive treponemal and reagin antibody tests will occur regularly in nonsyphilitic treponemal disease such as yaws and pinta.

mation in the detection of primary syphilis and/or reinfection. A four-fold or greater change in serial titers is highly significant and suggests recent acquisition of disease (10). Serial VDRL titers may be utilized to gauge the success of treatment. In contrast to the treponemal antibody tests which may remain positive for years or even for the patient's lifetime after adequate treatment of seropositive primary or secondary syphilis, the VDRL can be expected to decline in titer and eventually revert to negative following therapy (11). Successful treatment of a patient with seropositive primary syphilis results in conversion to VDRL negativity in about 75% of patients within 3–12 months and in nearly all patients by 24 months. The VDRL in treated secondary syphilis will become negative in 40% of patients at 12 months and in 75% of patients by 24 months. It is important to remember, however, that treatment of late infection may have little or no effect on VDRL titer (serofast) (23).

The best known treponemal antibody tests are the FTA-Abs, the MHA-TP and the TPI. The TPI was the first treponemal antibody test devised but because of technical difficulties and a requirement for a supply of live *T. pallidum,* it has been relegated to a few research laboratories and is not generally available to the practicing physician. For completeness, it is included in Table I. The FTA-Abs has replaced the TPI and is today the most widely used treponemal test. There has been a large clinical experience with this test performed with serum and it has been found to be both highly specific and sensitive. Confusion surrounding this test is consequent to its application to CSF and to a technical modification that allows selective identification of IgM treponemal antibody (FTA-Abs-IgM).

In order to improve upon the lack of sensitivity of the VDRL for the serological diagnosis of neurosyphilis, the FTA, FTA-Abs, and FTA-Abs-IgM have been applied to CSF. Most studies have suggested that the FTA is more often positive than the VDRL with CSF from patients with clinical neurosyphilis (5, 6, 21, 24). However, the FTA may be positive with CSF from syphilitics without clinical features of neurosyphilis and even with CSF obtained from control subjects who lack clinical evidence of syphilis and who have a negative serum FTA-Abs (6).

The FTA-Abs on the other hand has not demonstrated false positivity with CSF from nonsyphilitics but experience is still limited. The rate of positivity of this test with CSF from patients with neurosyphilis is less than the FTA (5, 6). The meaning of the test in syphilitics without

TABLE II

Recommendations for the Laboratory Diagnosis of Syphilis

Neonatal Congenital
1) Rising VDRL titer diagnostic
2) Positive FTA-Abs-IgM suggestive but not diagnostic (10% false positive)
   Negative FTA-Abs-IgM does not exclude diagnosis (35% false-negative) (7)

Primary
1) Darkfield examination of cutaneous lesion*
2) FTA-Abs more likely to be positive (85%) than either MHA-TP (65%) or VDRL (70%); a rising VDRL titer in the presence of a positive FTA-Abs is diagnostic.

Secondary
1) Darkfield examination of cutaneous lesion*
2) Positive VDRL in the presence of a positive FTA-Abs or MHA-TP

Late
- A. Latent, Late Benign and Cardiovascular
  1) Positive FTA-Abs or MHA-TP on serum** and a normal CSF examination. False positives may be excluded through repetition of the test in 6–12 months, or by the TPI (11, 19).
- B. Neurosyphilis
  1) Positive FTA-Abs or MHA-TP on serum** with CSF demonstrating any one or all of the following:
     a) ≥ 5 white cells/mm^3
     b) > 40 mg% protein
     c) Positive VDRL, (the FTA, or FTA-Abs on CSF is of uncertain significance at this time and therefore not recommended (20)).

* Darkfield examination may be unreliable on lesions in the mouth because *T. microdentium,* which is a member of the normal oral flora is morphologically indistinguishable from *T. pallidum.* In this situation, a darkfield examination of an aspirate from a regional lymph node would be preferable (10).

** VDRL is irrelevant, may be positive (70%) or negative (30%).

clinical or other laboratory features of neurosyphilis is unknown. The FTA-Abs-IgM has also been applied to CSF but it is so rarely positive that it appears to lack utility in this setting (5).

It was originally conjectured that the FTA-Abs-IgM would be the serologic test of choice for the neonate with suspected congenital syphilis. The serologic diagnosis of this stage of disease is hampered by the presence of transplacentally transferred maternal reaginic (VDRL) and treponemal (FTA-Abs) antibodies. Since maternal IgM does not cross the placenta it was reasoned that the FTA-Abs-IgM would signal the neonate's immunologic response to *T. pallidum.* Unfortunately initial enthusiasm for this test has been tempered by reports of up to 35% false negativity and 10% false positivity (7). False negatives occur particularly when the disease has been acquired late in gestation and there has been too little time for fetal antibody formation. The mechanism of production of false positives is unknown but it has been postulated that this phenomenon is related to IgM not directed at *T. pallidum* but rather to maternal IgG treponemal antibody (9).

The FTA-Abs test is not readily made quantitative and is subject to a variety of technical and interpretative errors (16, 17). Search for a simple, quantitative, and inexpensive treponemal antibody test led to the development of the MHA-TP test. This test is technically easier to perform than the FTA-Abs, is less subjective, and can be quantitated. Except for primary syphilis, the MHA-TP is as sensitive as the FTA-Abs for all stages (3, 12). Although, the occurrence of false-positive MHA-TP tests is usually less than 1.5% in control (normal)) populations, some studies have reported a rate of false positivity approaching 9% (3, 13). Additionally, the MHA-TP test may be false-positive more frequently than the FTA-Abs test with serum from individuals known to have a false-positive nontreponemal antibody test (3, 12, 15, 20). For these reasons it is recommended that a positive MHA-TP be confirmed by the FTA-Abs in cases in which the diagnosis of syphilis is clinically doubtful.

The MHA-TP is quantitative but surprisingly most studies have failed to demonstrate a practical relationship between MHA-TP titer and either clinical stage and progression of disease, titer of VDRL, or response to treatment. As many of these studies have evaluated only small numbers of patients, the full diagnostic and prognostic significance of MHA-TP titers remains to be assessed (12).

Definition of Terms

1) Neonatal congenital syphilis: Syphilis of the newborn acquired in utero.
2) Primary syphilis: The earliest stage of syphilis, occurring approximately three weeks after inoculation with *T. pallidum* and usually characterized by a single mucocutaneous lesion (chancre) associated with regional adenopathy.
3) Secondary syphilis: The stage of syphilis occurring approximately six weeks after the primary stage and usually characterized by symmetric mucocutaneous lesions and generalized lymphadenopathy; may include hepatitis, periostitis, iridocyclitis, arthritis, nephritis and other protean manifestations.
4) Late syphilis: The stage of syphilis following untreated secondary syphilis. This category encompasses:
   a) Latent syphilis—the stage of syphilis in which clinical signs or symptoms of disease are absent and the cerebrospinal fluid is normal
   b) Late benign syphilis—the stage of syphilis characterized by the presence of gummas (granulomas with surrounding perivascular infiltrate)
   c) Cardiovascular syphilis—the stage of syphilis characterized by endarteritis obliterans of vasa vasorum, potentially leading to aortitis, aortic

aneurysm formation, aortic insufficiency, or coronary ostial stenosis

d) Neurosyphilis—the stage of syphilis characterized by symptomatic or asymptomatic involvement of the central nervous system.

5) VDRL: The Veneral Disease Research Laboratory Test for nontreponemal (Reagin) antibody which has as an endpoint flocculation of a cholesterolized-cardiolipin-lecithin antigen.

6) FTA: The Fluorescent Treponemal Antibody Test for treponemal antibody detected by incubating serum (or CSF) with whole nonviable *T. pallidum* (Nichols strain) antigen fixed to a glass slide and made fluorescent (visible) by the addition of fluorescein conjugated antihuman globulin.

7) FTA-Abs: The Fluorescent Treponemal Antibody Absorption Test performed as in FTA above but with the additional step of first diluting the serum (or CSF) in a "sorbent" prepared from Reiter strain treponema in order to absorb out cross-reacting group antibody induced by saprophytic nonpathogenic treponemes.

8) FTA-Abs-IgM: The Fluorescent Treponemal Antibody Absorption Test for IgM treponemal antibody performed as in FTA-Abs above except a specific anti-IgM fluorescinated conjugate is used.

9) MHA-TP: The Microhemagglutination Assay for *T. pallidum* performed by absorbing serum (or CSF) with sorbent and then incubating with erythrocytes sensitized with cellular components of Nichols strain of *T. pallidum.* In the presence of treponemal antibody agglutination of erythrocytes occurs.

10) TPI: The *Treponema pallidum* Immobilization Test performed by incubating live motile *T. pallidum* with serum and complement. Immobilization of the treponemes occurs in the presence of treponemal antibody.

11) Prozone phenomenon: The inhibition of precipitation of antigen—antibody complexes by extreme antibody excess.

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Crohn's Ileocolitis, Cutaneous Gangrene and Cryoglobulinema

ALAN ALTMAN, M.D., SAMUEL MEYERS, M.D., DAVID B. SACHAR, M.D., AND, HENRY D. JANOWITZ, M.D.

Abstract

A 38-year-old female patient with a ten-year history of Crohn's ileocolitis established by clinical, radiographic, endoscopic and histologic findings is presented. She demonstrated cold sensitivity, Raynaud's phenomenon, arthralgias, nephritis, thromboembolism and significant cutaneous gangrene. It is suggested that her extraintestinal complications are associated with and a consequence of, a cryoglobulin isolated from the serum.

Necrotizing skin lesions are uncommon complications of inflammatory bowel disease (1, 2). In our review of 700 patients treated at The Mount Sinai Hospital between 1964 and 1973, this complication was not noted (3). Cryoglobulins and cryofibrinogens have been demonstrated in ulcerative colitis patients, the latter being incriminated as the cause of skin necrosis (4, 5). We report the presence of a cryoglobulin and associated cutaneous gangrene in Crohn's disease.

Case Report

A 38-year-old Caucasian housewife was admitted to The Mount Sinai Hospital with Crohn's ileocolitis of ten years duration, that had been in remission over the preceding two years. Over the past several years, she had suffered from arthralgias, migratory thrombophlebitis, and Raynaud's phenomenon, especially during the winter months. Six months prior to admission, she developed indolent painful ulcerations on her ankles, buttocks, and fingertips, associated with a bluish discoloration of hands and feet. Therapy with 60 mg prednisone per day was initiated. Several weeks later, an acute pulmonary embolus necessitated the addition of coumadin anticoagulation. No further cutaneous ulcerations developed but established lesions persisted and, in fact, progressive pain and necrosis of the distal phalanx of her left index finger occurred.

Physical examination showed an afebrile, Cushingoid woman. There was acrocyanosis of both hands and feet, and the distal phalanx of the left index finger was dry and necrotic (Fig. 1). Scattered cutaneous ulcerations

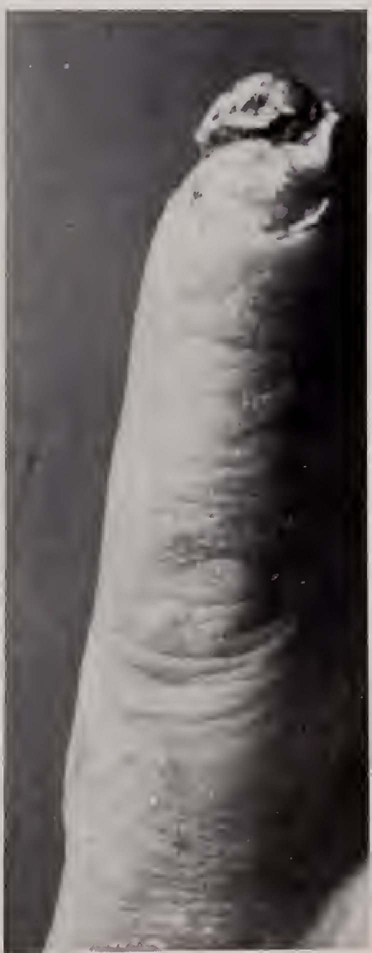

Fig. 1: Necrotic distal phalanx of left index finger.

From the Division of Gastroenterology, Department of Medicine, The Mount Sinai Hospital and Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to Samual Meyers, M.D., Division of Gastroenterology, Annenberg 23-08, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, N.Y. 10029.

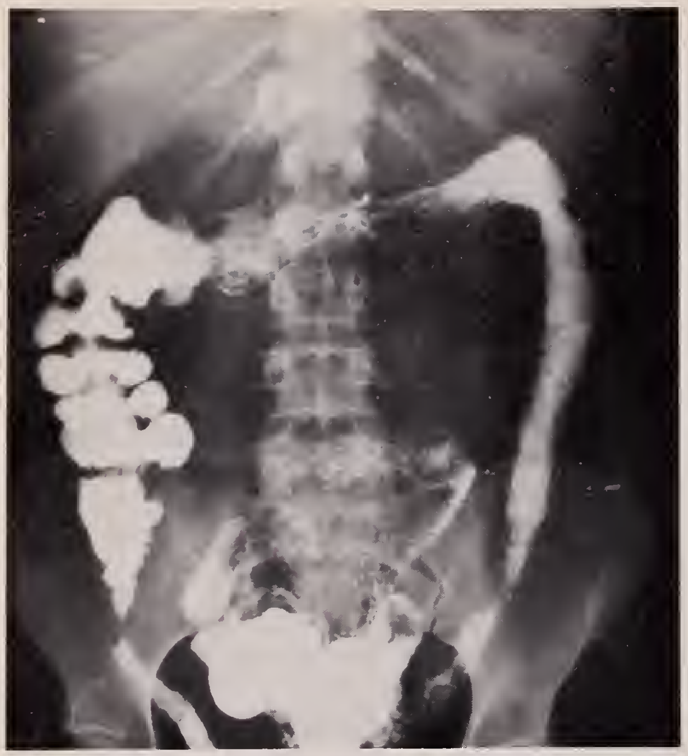

Fig. 2: Barium enema demonstrating Crohn's ileocolitis.

were present on the hands, lateral malleolus of the right ankle and buttocks. All pulses were present and normal in character. There was no lymphadenopathy nor hepatosplenomegaly.

The hemoglobin was 12g/dl, white blood cell count was 10,000/mm^3 with a normal differential count, platelet count was 340,000/mm^3 and erythrocyte sedimentation rate was 32mm/hr. Routine blood chemistries were normal. Urinalysis revealed 2$^+$ proteinuria, numerous red and white blood cells and hyaline casts. Twenty-four hour urine protein was 1.9 g, creatinine clearance 98 cc/minute. Urine and blood cultures were negative. The following special tests were negative or normal: venereal disease research laboratory test (VDRL), antinuclear antibody, latex fixation, antistreptolysin O titer, cold agglutinin titer, HB$_s$ag, total serum complement, prothrombin time, partial thromboplastin time (prior to initiation of coumadin therapy), fibrin split products, serum viscosity, serum protein electrophoresis and immunoelectrophoresis. Urine protein immunoelectrophoresis showed a nonselective pattern; Bence-Jones proteins were not demonstrated. Chest x-ray was normal. No immunoglobulin G, M, A or third component of complement was detected by standard fluorescent antibody technique using specific antisera (Behringwerke

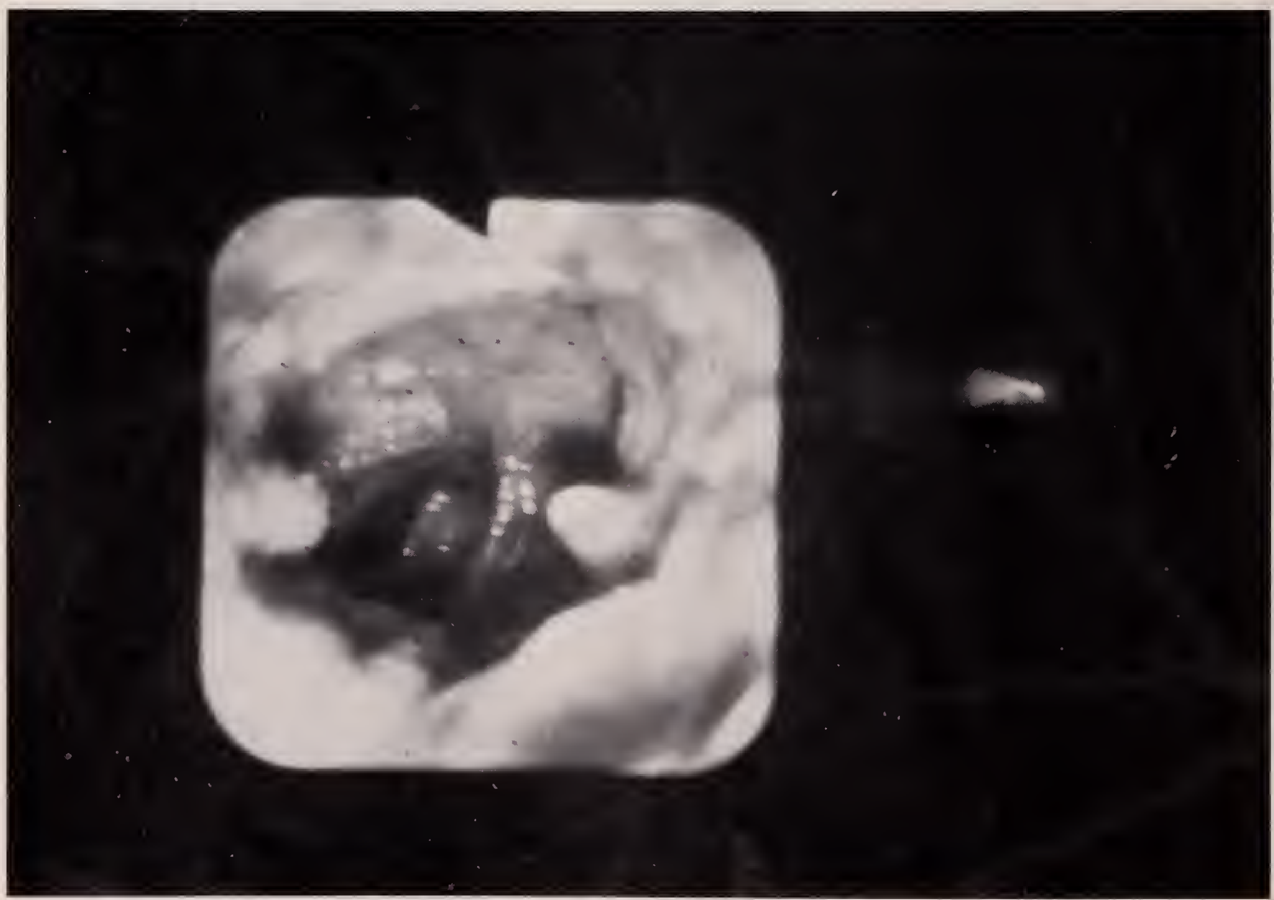

Fig. 3: Colonoscopic appearance of descending colon.

AG, Marburg, W. Germany). The specificity of the fluoresceinated antisera was determined by staining of myelomatous tissue.

Venous blood was collected in a plain glass tube, maintained and centrifuged at 37° C. The supernatant was separated and incubated 72 hours at 4° C. During this time, a cryoglobulin precipitated, the amount of which was insufficient for further characterization. The SIA test of serum was positive.

Barium enema, small intestinal x-rays and colonoscopy demonstrated the typical abnormalities of Crohn's ileocolitis (6, 7). The bowel was diseased from the terminal ileum to the proximal rectum (Fig. 2, 3). Colonoscopic biopsies showed diffuse chronic inflammatory infiltrate; the mucosal glands and their goblet cell populations were relatively normal. Vascular structures were normal, with no evidence of vasculitis.

Discussion

Necrotizing cutaneous lesions have been reported in ulcerative colitis; these cutaneous lesions represented a vasculitis of uncertain etiology (1, 2). Cryoproteins, although not demonstrated in these particular patients, may result in similar cutaneous lesions (8). Indeed, this phenomenon recently has been reported in ulcerative colitis, where a blood cryofibrinogen was identified in a patient with skin necrosis (5). Polcak et al noted that 118 of 164 patients with ulcerative colitis at their institution had disease exacerbation with cold exposure (4). A mixed IgG-IgM cryoglobulin was identified in 92 of these subjects, yet none had necrotizing skin lesions.

Essential cryoglobulinemia may result in an ileocolitis resembling Crohn's disease (9). In our patient however, the primary disorder appeared to be Crohn's ileocolitis with a secondary cryoglobulinemia. This formulation is supported by the presence of radiographic, colonoscopic and histologic criteria of Crohn's disease (6, 7, 10). The defining features of a vasculitis, including vascular fibrinoid necrosis and polymorphonuclear cell infiltration, were not present in the colonic biopsies from our patient. Other possible causes of her cryoglobulinemia, including lymphoproliferative disorders, plasma cell dyscrasia, collagen diseases, and hepatitis infection, were excluded (8, 11–13).

The presence of the cryoglobulin could account for her cutaneous gangrene as well as for her Raynaud's phenomenon, arthralgias, nephritis, and thromboembolism (8). Neither the small amount of cryoglobulin isolated, nor the failure to identify immunoglobulin in the skin biopsy, militates against a pathogenetic role for the cryoprotein. Brout et al report similarly low levels in one third of their cases of essential mixed cryoglobulinemia, all of whom had prominent symptomatology (8). Immunoglobulin stains in skin tissue are most frequently positive when lesions are present less than 24 hours (14, 15). Our patient, who was on corticosteroid therapy, had no such fresh lesions at the time of biopsy.

A broad spectrum of bacterial and other antigens has access to the systemic circulation through the abnormal gut in patients with inflammatory bowel disease (16). This continued antigenic provocation may be important in the pathogenesis of the observed cryoglobulinemia (17). Once present, cryoglobulins cause their associated symptoms by vascular obstruction and/or induction of vascular inflammation, in a manner similar to immune complexes (9).

There are no controlled trials available to guide therapy of cryoglobulinemia. Our patient's inflammatory bowel disease was in remission and required no specific therapy. Anticoagulation was instituted in view of her thromboembolism. Corticosteroids and immunosuppressive agents have been reported to be of use (18). Steroids alone in our case appeared to halt the appearance of new cutaneous lesions, but there was no apparent benefit to the established lesions. Other reported therapeutic modalities have included plasmapheresis, penicillamine, and hydroxychloroquine (8, 19, 20).

We suggest that any patient with inflammatory bowel disease and cold sensitivity, or with other symptoms suggestive of the presence of a cryoprotein, be evaluated for this complication. Prompt identification and therapy may diminish potential morbidity.

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Ultrastructural Features of a Malignant Giant Cell Tumor of Bone with Areas of Osteogenic Sarcoma

A. K. M. SHAMSUDDIN, M.D.*, V. A. VARMA, M.D.*, C. TOKER, M.D.* AND CHARLES C. EDWARDS, M.D.†

Abstract

Light and electron microscopic features are described in a case of malignant giant cell tumor of bone that had focal areas of osteogenic sarcoma. By electron microscopy, the principal cell types of the malignant giant cell tumor were (a) Stromal mono or binucleated cells with bizarre nuclei, multiple nucleoli and variable profiles of dilated endoplasmic reticulum; (b) Giant cells containing a variable number of nuclei showing marked pseudoinclusions, 40–60Å thin filaments and centrioles; (c) Mononuclear cells with very scanty organelles. The osteogenic sarcomatous areas showed abundant osteoid and malignant osteoblasts in and around the osteoid. The osteoblasts contained variable profiles of dilated endoplasmic reticulum and 40–60Å thin filaments. There was no distinct ultrastructural difference between the morphology of the stromal cells of the giant cell tumor component and the osteoblastic cells of the osteogenic sarcoma. We, therefore, suggest that the osteogenic sarcomatous component has resulted from sarcomatous transformation of giant cell tumor.

Introduction

Giant cell tumors of bone are relatively uncommon neoplasms but their malignant counterpart are even less common. Ultrastructural features of Grade I or conventional giant cell tumors have been well documented by Steiner et al (10). Ultrastructural characteristics of osteogenic sarcomas have also been described recently by Williams et al from a review of twenty cases (12). This report describes the transmission electron microscopic features of a malignant giant cell tumor of bone that showed distinct foci of osteogenic sarcoma. Ultrastructural morphology of the principal cell types of the two lesions occurring in the same tumor are compared. The ultrastructural study confirmed the light microscopic diagnosis and this is the first report of electron microscopic features of this tumor.

Case Report

A 21-year-old pregnant white female was well until October 1977, when she fell on her right knee and noted a progressive swelling. Radiologic examination showed a large expansile lytic lesion involving the lower metaphysis and epiphysis of the femur; the proximal margin was ill defined and a minimal periosteal reaction was noted (Fig. 1). Biopsy showed a large number of giant cells scattered in a cellular stroma. The stromal cells showed marked pleomorphism with abundant mitotic figures. Scattered osteoid production was evident. The patient suffered a pathologic fracture and subsequently a right above knee amputation was performed on November 12, 1977. Five months after surgery, the patient is currently undergoing adjuvant chemotherapy. The patient does not show any evidence of residual or metastatic malignancy currently.

Gross examination of the amputated limb showed a large expansile cystic mass involving the lower 14 cm of the femur including both the condyles and extending up to the articular cartilage and measuring 11 cm in greatest dimension. The surrounding bony capsule was 2–5 mm in thickness. The lesion was soft in consistency with gray-brown color and showed areas of hemorrhage and degeneration (Fig. 2).

Materials and Methods

Light Microscopy:

After obtaining samples for electron microscopy, the tissues were fixed in 10% buffered formalin, embedded in paraffin and stained with hematoxylin and eosin.

From the Departments of Pathology* and Orthopedic Surgery,† University of Maryland School of Medicine, Baltimore, Md.

Requests for reprints should be sent to A. K. M. Shamsuddin, M.D., Department of Pathology, University of Maryland School of Medicine, Baltimore, Md. 21201.

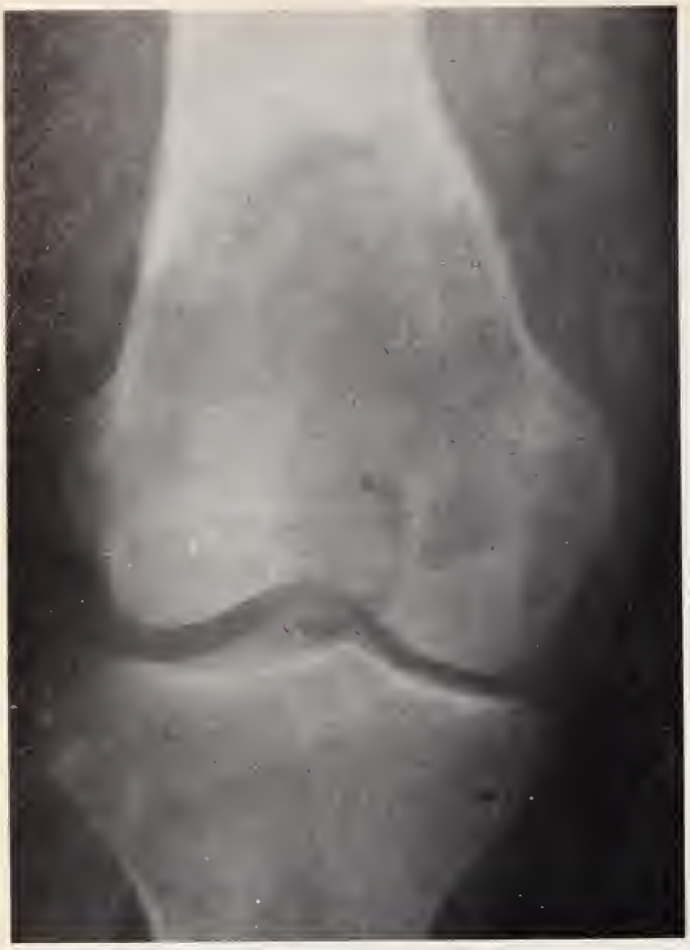

FIG. 1 Roentgenogram showing large expansile mass involving the metaphysis and epiphysis with extension up to the articular cartilage.

Electron Microscopy:

Fresh tissues were obtained directly from the pale gray areas of grossly viable tumor, and small pieces were immediately fixed in 4% formaldehyde, 1% glutaraldehyde mixture (6). After adequate fixation, the sections were washed with sucrose cacodylate buffer, osmicated, stained en-bloc with uranyl acetate, dehydrated with graded ethanol and embedded in Epon-812. One thousand angstrom thick sections were stained with toluidine blue. Areas of malignant giant cell tumor and osteogenic sarcoma were selected for thin sectioning. The 600-800Å thin sections were stained with uranyl acetate and lead citrate and examined with a Jeol-100B electron microscope at 60 KV.

Results

Light Microscopy:

Two distinct patterns were observed in this tumor-one, characteristic of the malignant giant cell tumor of bone and the other, showing features typical of osteogenic sarcoma. Transitional areas were also present.

The malignant giant cell tumor component showed numerous large multinucleated giant cells with spindle shaped mononuclear stromal cells. The giant cells contained 3-35 bizarre nuclei and multiple nucleoli. The stromal spindle cells showed marked pleomorphism of both nuclei and cytoplasm. There were bizarre nuclei which were one to three in number and mitotic figures were abundant. Cells intermediate between the stromal spindle cells and large multinucleated giant cells were also seen (Fig. 3 and 4).

Foci of osteogenic sarcoma showed abundant pink eosinophilic osteoid lined by malignant osteoblasts showing nuclear and cytoplasmic pleomorphism (Fig. 5).

Transitional areas between the two distinct lesions described above were seen where there were scanty osteoid and smaller multinucleated giant cells. The stromal cells were indistinguishable from those of either of the two lesions. Examination of the hemorrhagic areas showed large blood filled spaces lined by giant cells and pleomorphic cells.

Electron Microscopy:

I. Malignant Giant Cell Tumor Component: Typical areas of malignant giant cell tumor were selected by light

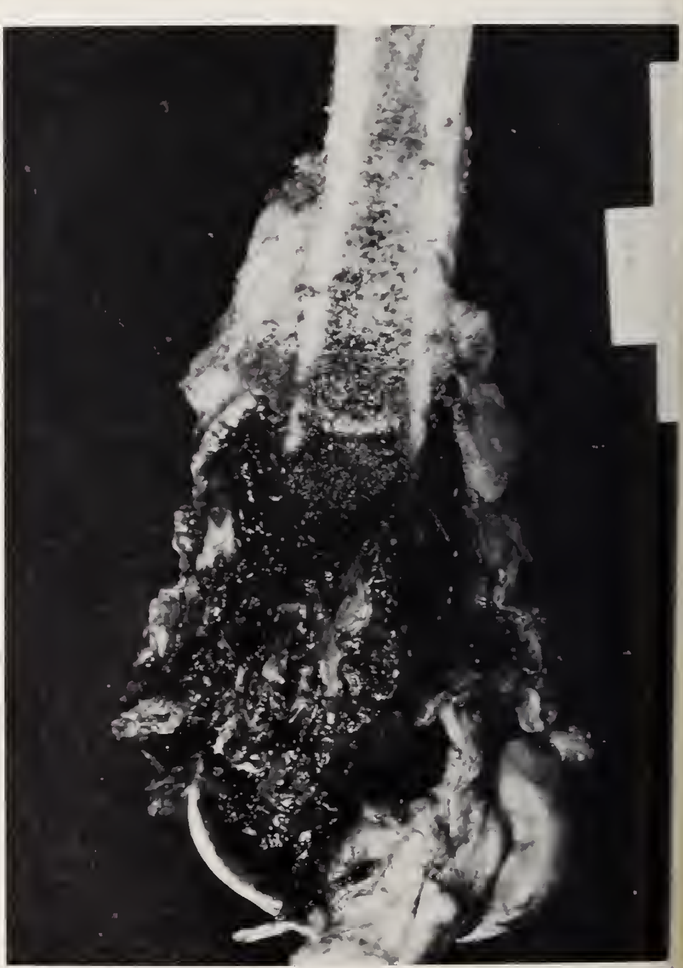

FIG. 2 Longitudinal section of the amputated extremity showir expansile nature of the growth and extension up to the articular surfac Gray-white tumor tissue along with hemorrhagic areas are seen.

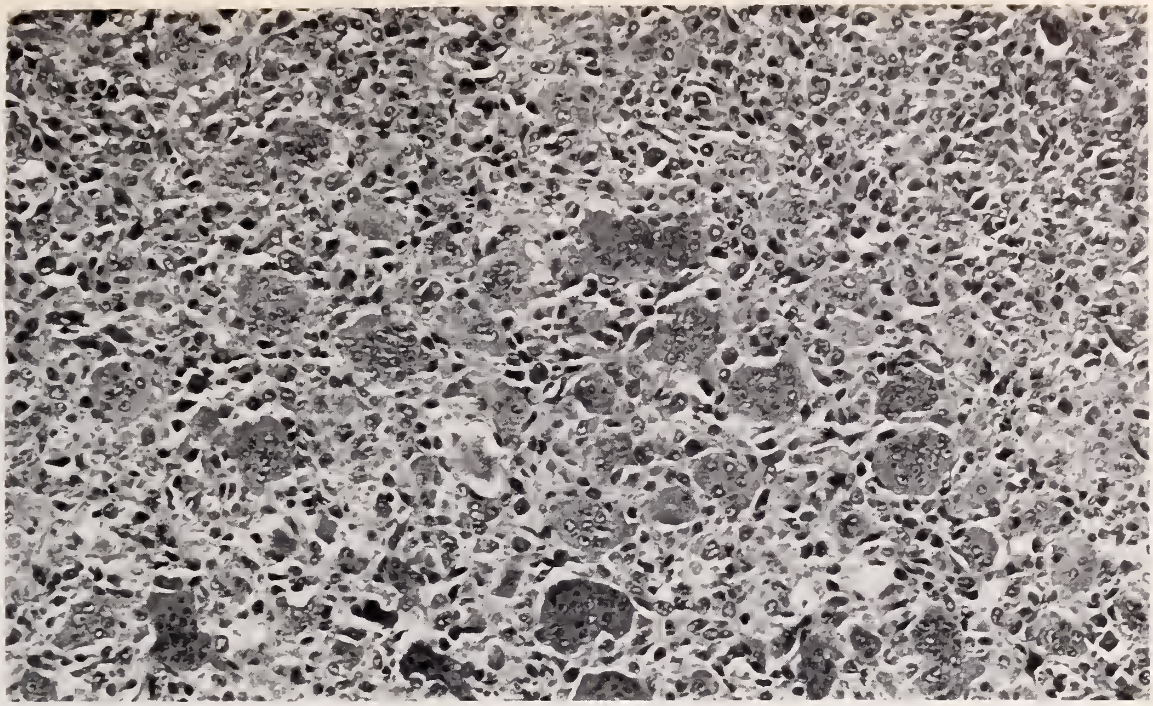

FIG. 3 Malignant giant cell tumor component: Numerous multinucleated giant cells and stromal spindle cells as seen here predominate the histology.

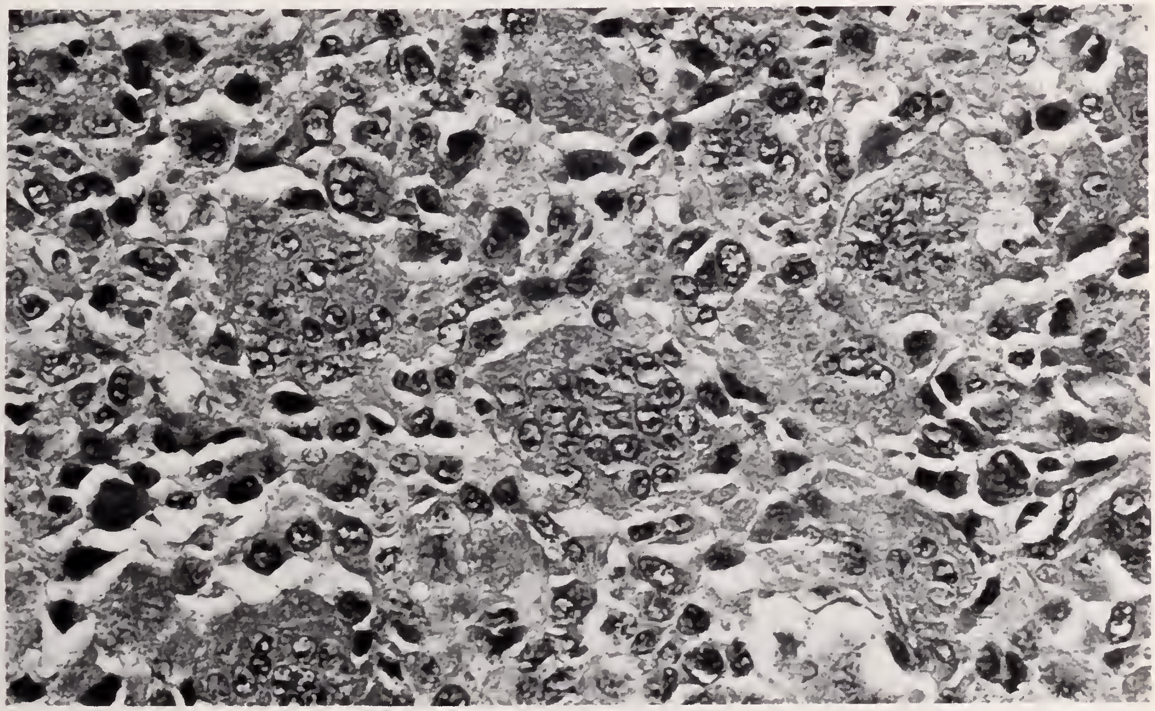

FIG. 4 Higher magnification of Fig. 3 showing pleomorphic and bizarre stromal cells.

icroscopic examination of 1000Å thick sections (Fig. 6). ltrastructurally, three cell types were observed.

a. *Giant cells*: The cell membranes were irregular and ffled with microvillous-like projections. Close apposiion was observed to adjacent cells. Except for occasional termediate junctions, most of the apposed cell membranes did not show a substantial number of cell junctions (Fig. 7). Although the cytoplasm contained a variable proportion of organelles, there were, by and large, abundant mitochondria (Figs. 8 and 9). Occasional profiles of dilated rough endoplasmic reticulum containing slightly electrondense fibrillar material in the cisternae were seen. Forty to sixty angstrom thin filaments were seen both in the central and peripheral parts of the cytoplasm. Primary lysosomes, lipid vacuoles and centrioles were also seen. The latter (Fig. 8 inset) were located both in the peripheral as well as in the central areas of the cytoplasm. The nuclei of most of the giant cells examined appeared bizarre with marked cytoplasmic invaginations of the nuclear membrane. The nucleoli, often multiple, were large and irregular.

b. *Spindle cells*: The principal stromal cells were spin-

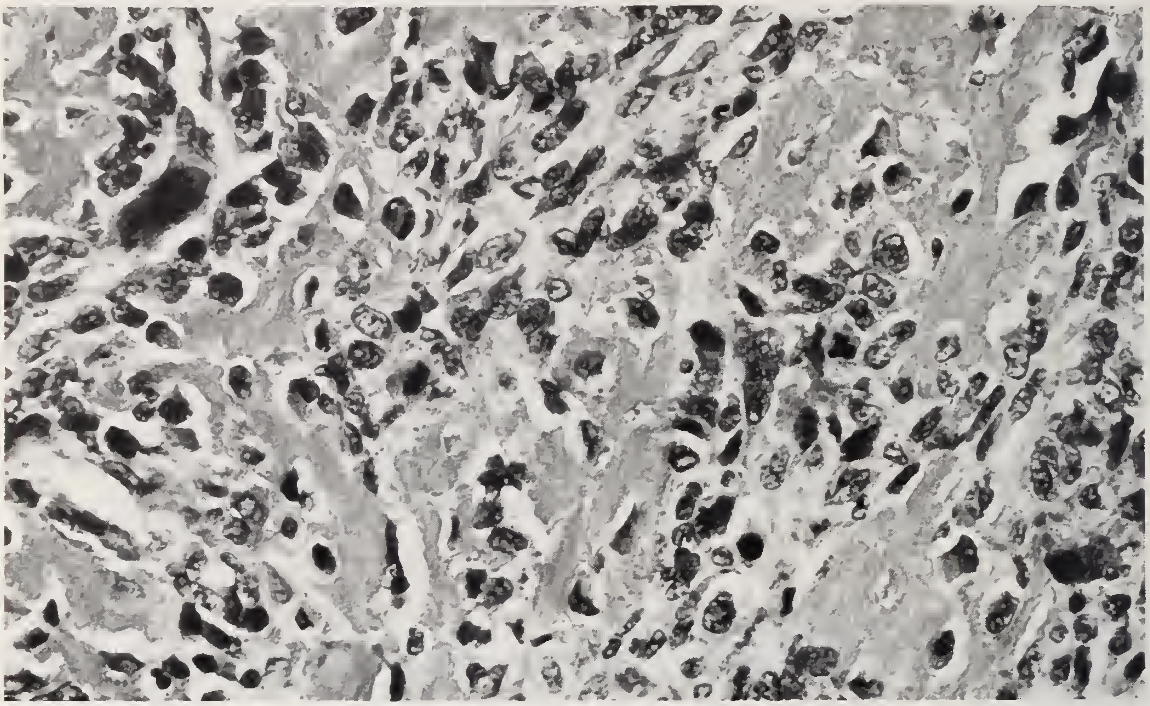

FIG. 5 Osteogenic sarcoma component showing an area of neoplastic osteoid lined by malignant osteoblasts. One large osteoblast with hug nucleus is seen at the upper left-hand corner of the picture. A tripolar mitotic figure is seen at the right-hand side, halfway from the center.

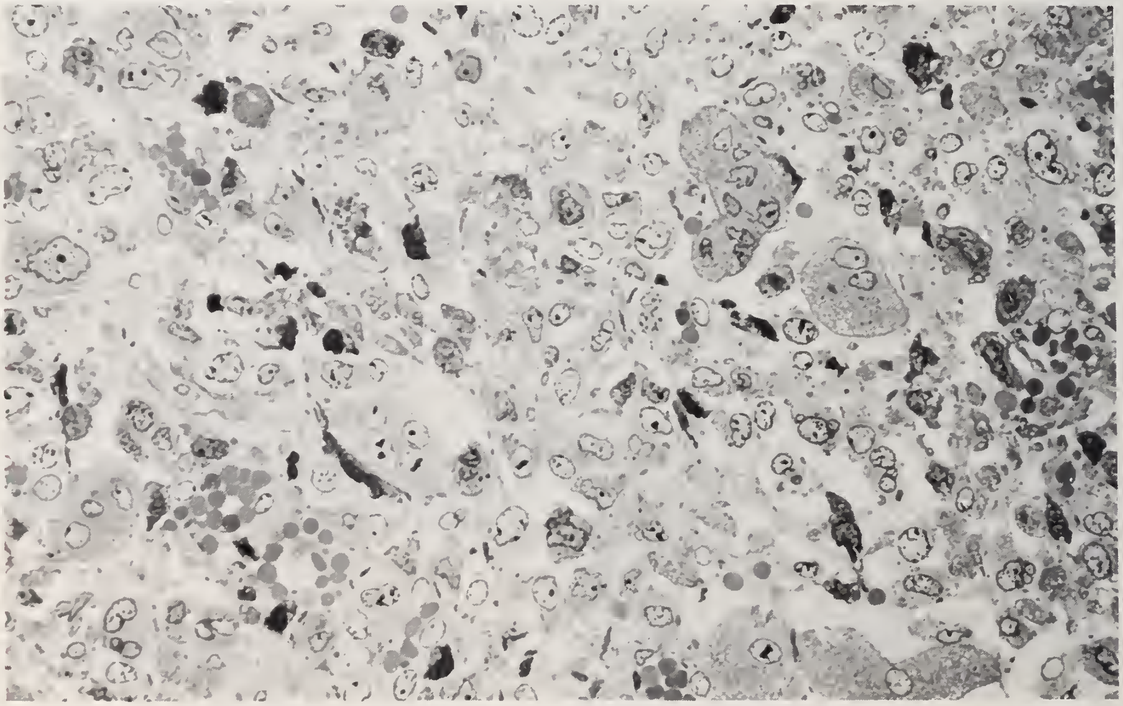

FIG. 6 Epon-embedded 1 micron section showing a typical area of malignant giant cell tumor. Electron micrographs shown in Fig. 7 throu Fig. 13 are from such areas. (Toluidine blue)

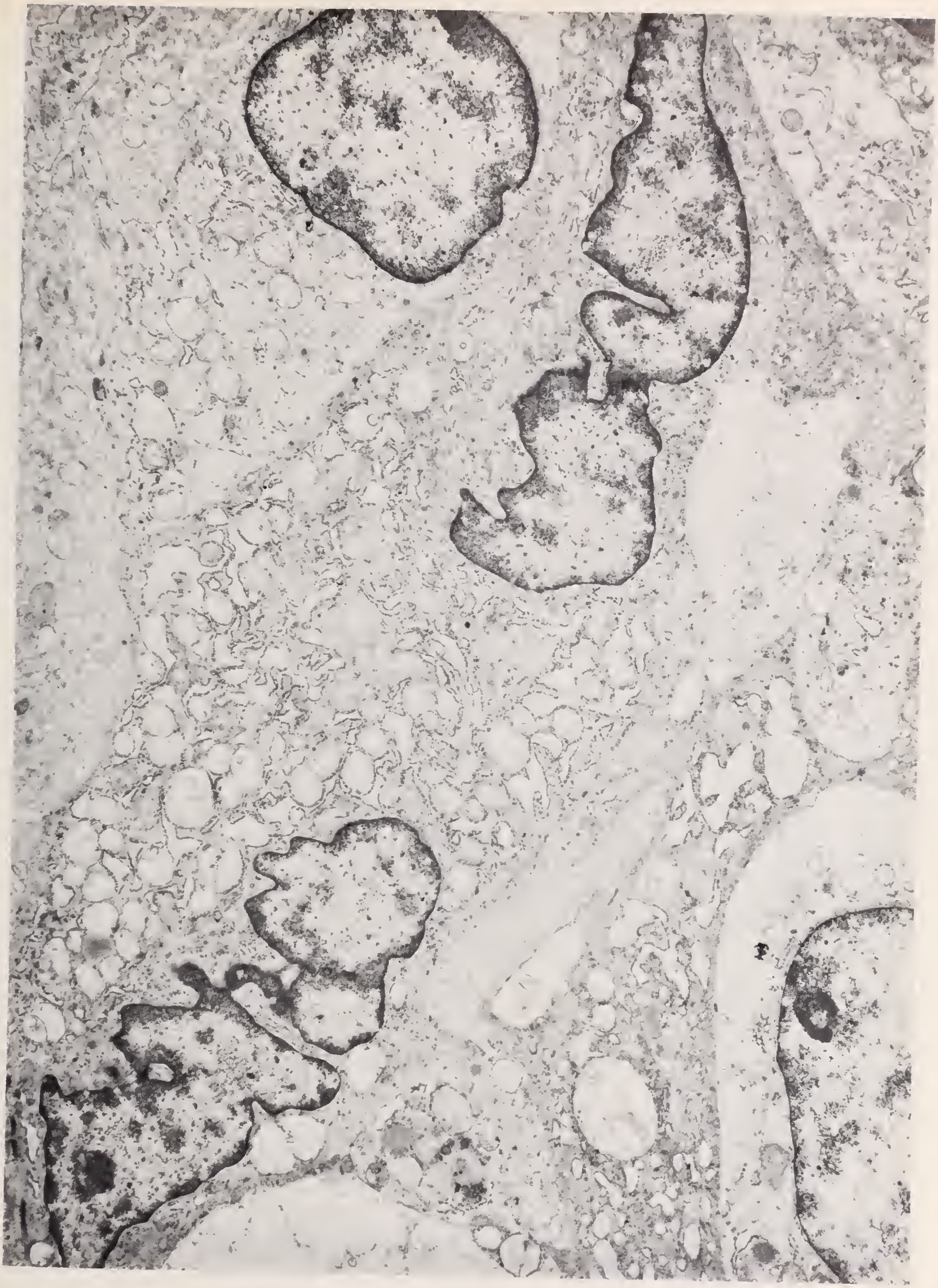

FIG. 7 A large spindle-shaped binucleated cell considered to be an early form of giant cell is shown with lipid vacuole and abundant dilated ough endoplasmic reticulum. Well formed desmosomes are seen at the lower left-hand corner. (Malignant giant cell tumor component, × 7,500)

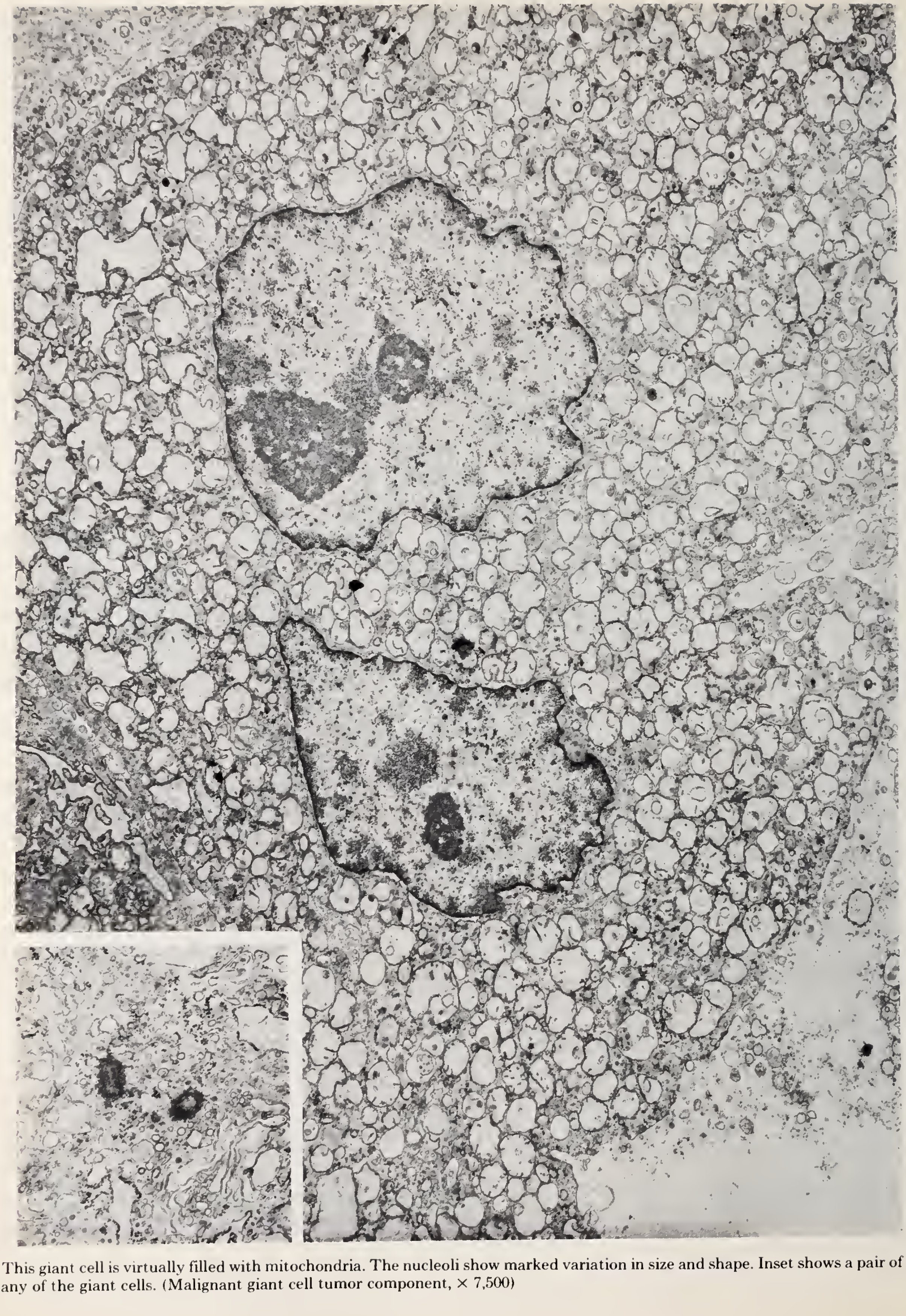

FIG. 8 This giant cell is virtually filled with mitochondria. The nucleoli show marked variation in size and shape. Inset shows a pair of centrioles seen in many of the giant cells. (Malignant giant cell tumor component, × 7,500)

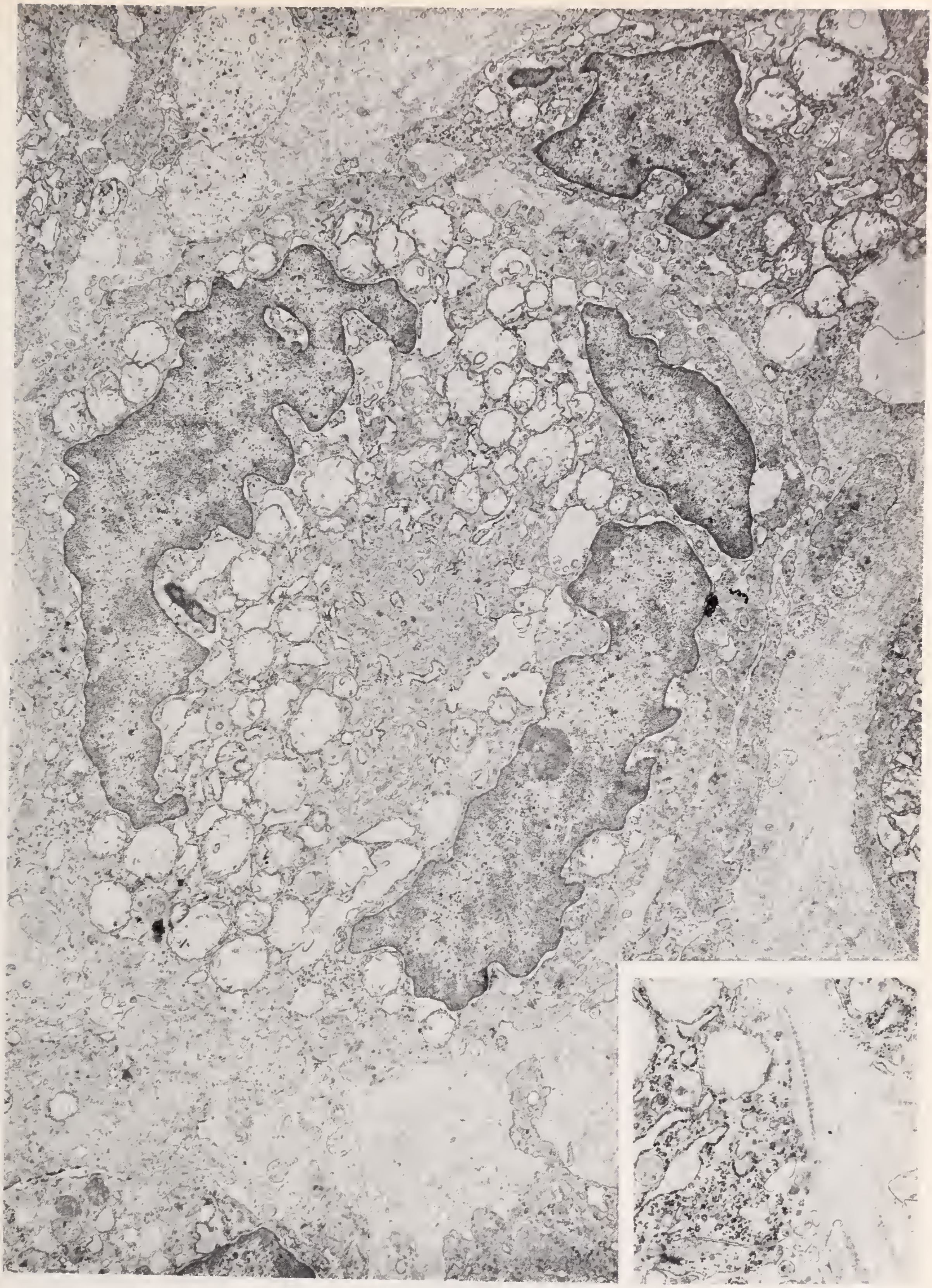

Fig. 9 This giant cell shows a central area containing few organelles. Inset shows collagen fibers in the stroma. (Malignant giant cell tumor component, × 7,500)

dle shaped with abundant organelles rendering the cytoplasm fairly electron dense. The cell membranes were regular. Areas suggestive of desmosomal sites were observed between the spindle cells (Fig. 10) and also between these and the giant cells (Fig. 7). The cytoplasm contained a variable amount of organelles; in some, there was an absolute paucity while in others, there were a moderate number of mitochondria, dilated cisternae of

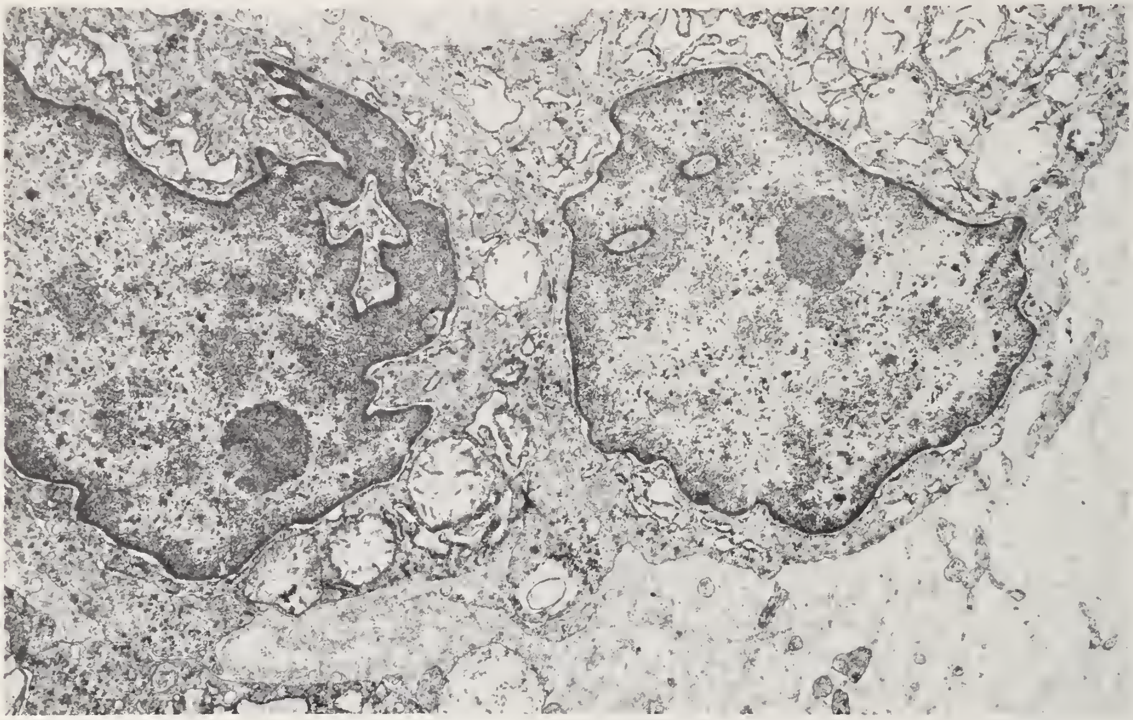

FIG. 10 Two stromal spindle cells showing nuclear pseudoinclusions and prominent nucleoli. Specialized area of plasma membrane resembling a cell junction is seen between the two cells at the center of the field. (Malignant giant cell tumor component, × 3,000)

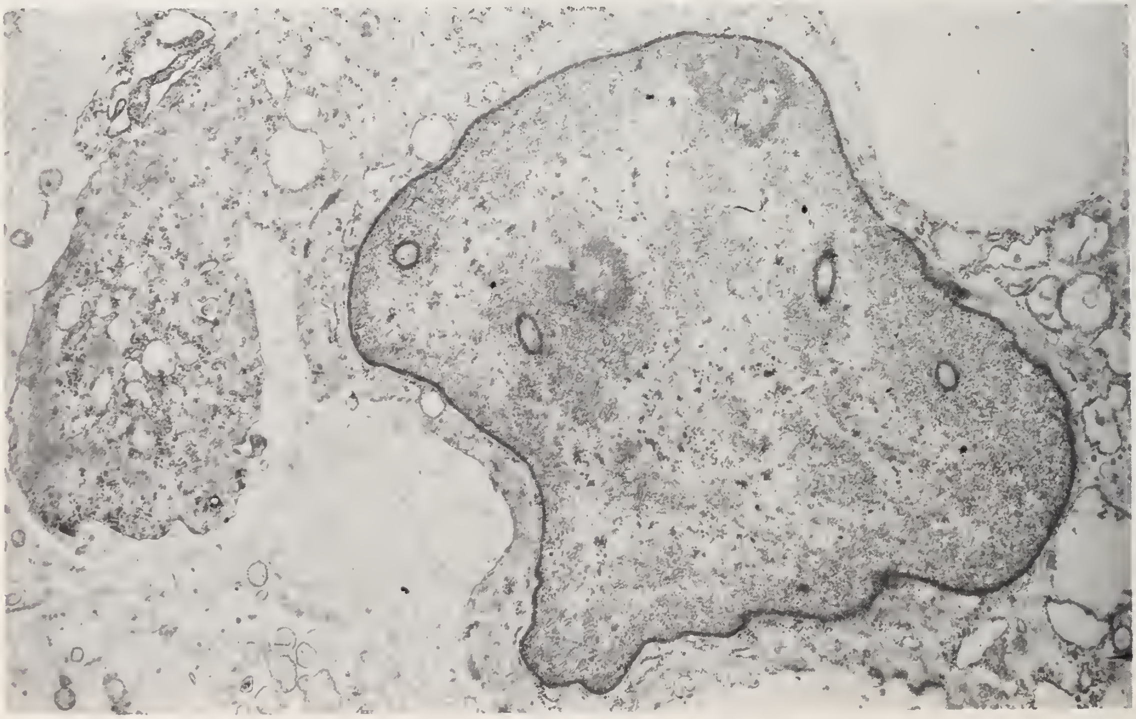

FIG. 11 Stromal spindle cell showing very little organelle. The nucleus shows two nucleoli and multiple pseudoinclusions. (Malignant giant cell tumor component, × 3,750)

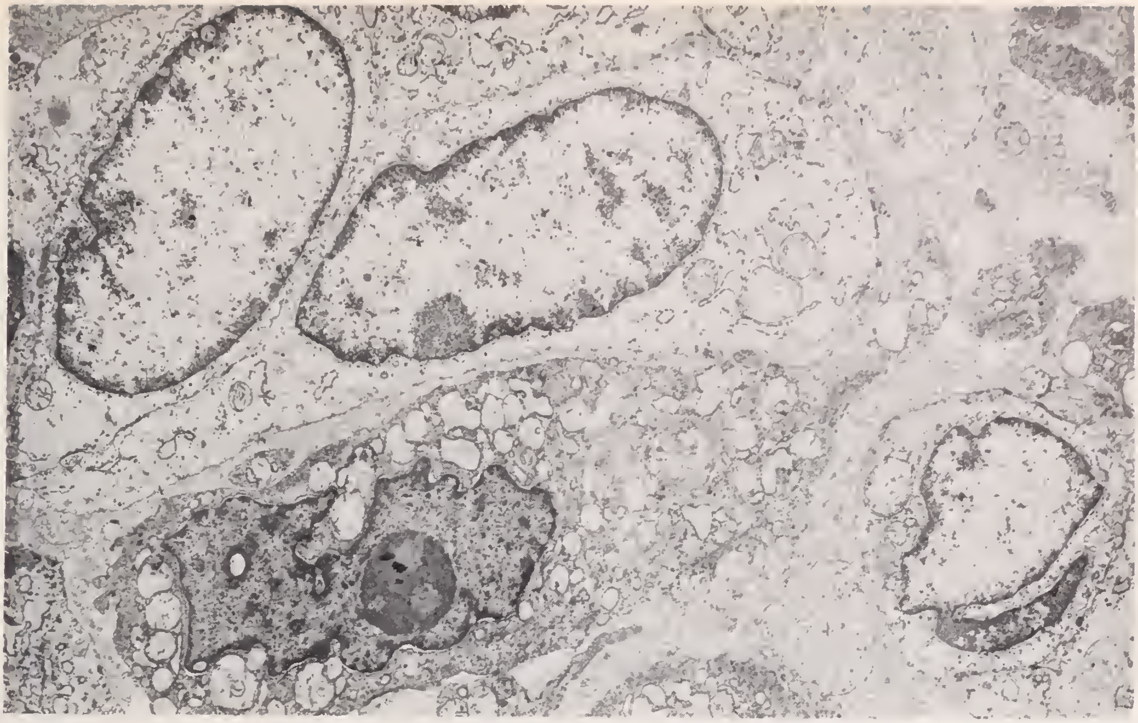

FIG. 12 Two cells with electron-lucent cytoplasm and scanty organelles, are seen along with a malignant appearing spindle cell. (Malignant giant cell tumor component, × 3,000)

rough endoplasmic reticulum and rare Golgi profiles. The nuclei showed marked pseudoinclusions and prominent nucleoli (Fig. 11).

Cells having morphologic features intermediate between these two principal types were seen containing two to four nuclei, abundant microfilaments, rough endoplasmic reticulum and mitochondria.

c. *Light mononuclear cells*: A less frequent type of stromal cell was seen which had relatively light electron-lucent cytoplasm with very scanty organelles–two to three mitochondria, uniform nucleus, and regular cell membrane (Fig. 12).

Intercellular Space: The intercellular space consisted mostly of mildly electron-dense nonfibrillar material with rare collagen fibers having 600Å periodicity (Fig. 9 inset).

II. *Osteogenic Sarcomatous Component*: Areas of osteogenic sarcoma were selected by light microscopy (Fig. 13). The principal cell type was the malignant osteoblasts that contained a variable amount of organelles. These cells were seen in and around the osteoid. The cell membrane was slightly irregular, but not ruffled. There was a variable profile of dilated endoplasmic reticulum; 40-60Å thin filaments and primary lysosomes were also seen. The nuclei showed less marked indentations (Figs. 14, 15).

The stromal osteoid was composed mostly of collagen fibers with periodicity of 600Å. No evidence of calcification or early hydroxyapatite crystal formation was seen n any of the blocks examined.

Discussion

Ultrastructural features of the malignant giant cell tumor component and the osteogenic sarcoma component in a single tumor are described. The clinical history, radiological, gross and light microscopic features, supplemented by ultrastructural study, suggest that the predominant component of the lesion is the malignant giant cell tumor. The multinucleated giant cells with abundant mitochondria, sparse rough endoplasmic reticulum, lysosomes and centrioles, are similar to those described in previous reports (3, 10). The principal stromal cells with abundant dilated endoplasmic reticulum, and the light mononuclear cells with very few organelles seen in this tumor, have also been described in Grade I giant cell tumor of bone by Steiner et al (10). The pleomorphic and bizarre appearance of nuclei with pseudoinclusions seen in the giant cells, the stromal spindle cells, and in cells intermediate in type between these two, fulfill the light and electron microscopic criteria of the malignant giant cell tumor of bone.

On the contrary, neither the clinical history, nor the radiologic appearance strongly suggest the diagnosis of a primary osteogenic sarcoma in this patient. However, the foci of characteristic abundant neoplastic osteoid with malignant osteoblasts, seen both by light and electron microscopy, point to the fact that the malignant giant cell tumor component is the initial and the predominant lesion while the osteogenic sarcoma is a late component.

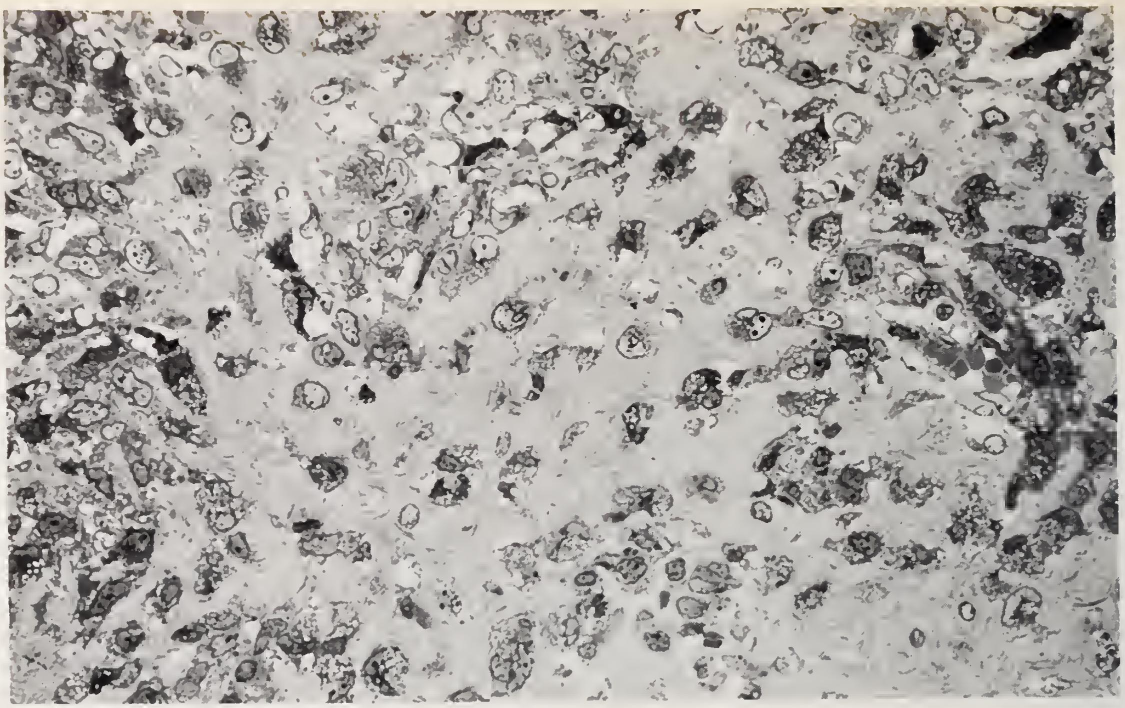

FIG. 13 Epon-embedded 1 micron section of osteogenic sarcoma component showing abundant osteoid and pleomorphic osteoblasts. Electron micrographs shown in Fig. 14 and Fig. 15 are from such areas. (Toluidine blue)

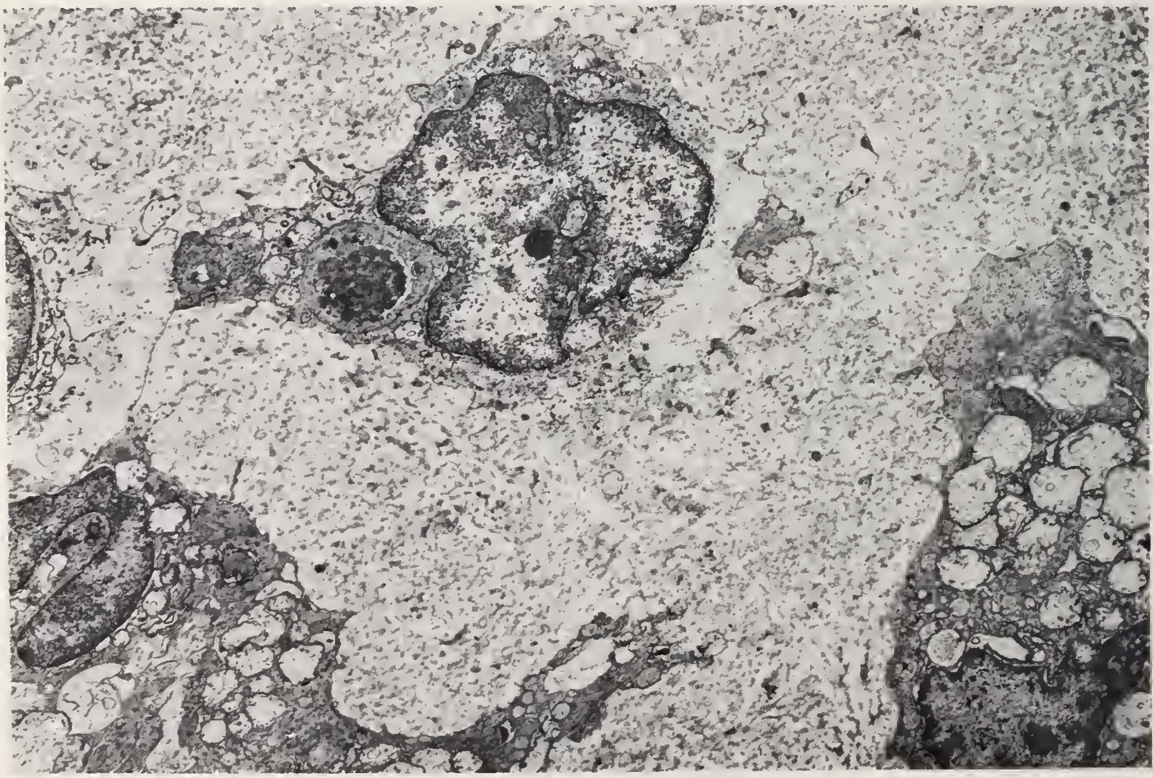

FIG. 14 An osteoblast and portions of two more are seen in an area of osteoid. A large secondary lysosome is seen in the osteoblast. N evidence of calcification can be seen. (Osteogenic sarcoma component, × 3,000)

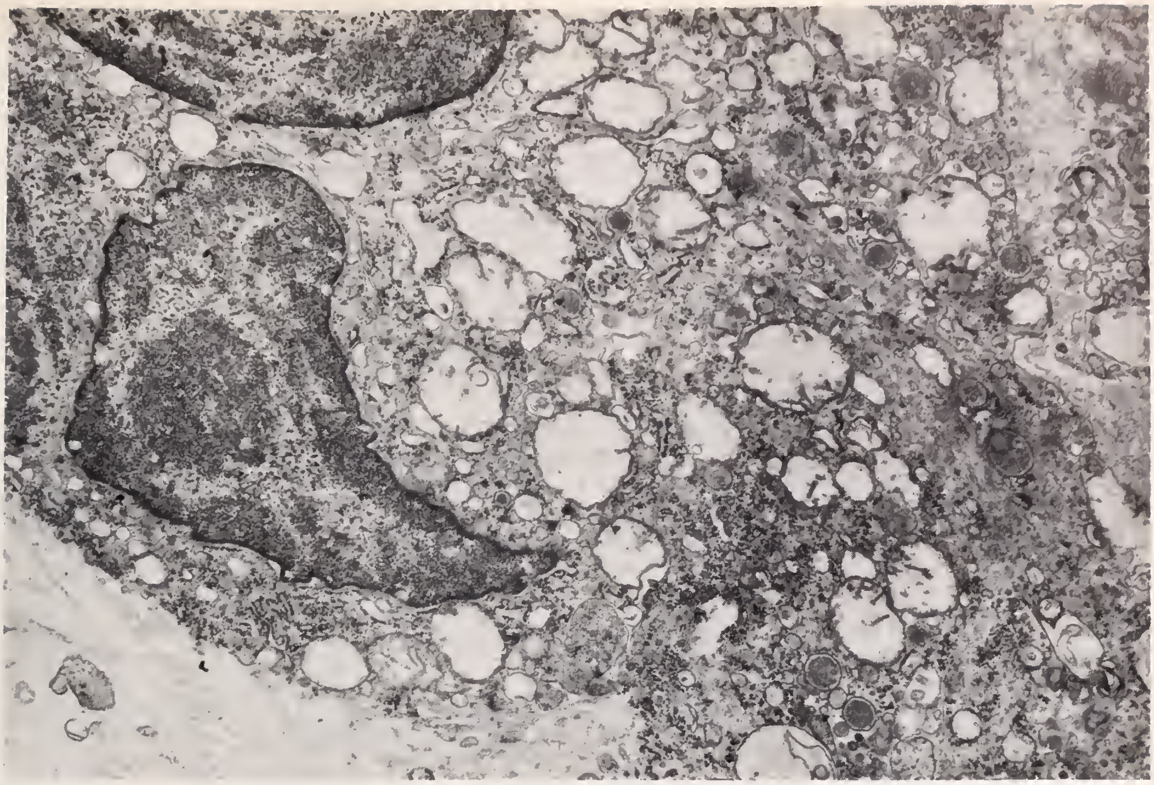

FIG. 15 Higher magnification view of osteoblasts showing lysosomes, polysomes, thin filaments and occasional dilated cisternae of rough endoplasmic reticulum. Collagen fibers of osteoid are seen at the lower left-hand corner. (Osteogenic sarcoma component, × 16,000)

Although no sequential morphologic changes can be demonstrated, nevertheless, the presence of transitional areas showing scanty osteoid, "small" giant cells, and pleomorphic stromal spindle cells also suggest that the osteogenic sarcoma component is the late or transformed element in a primary malignant giant cell tumor.

No definite morphologic difference between the stromal spindle cells of giant cell tumor component and the osteoblasts of the osteosarcoma component has been seen either by light or by electron microscopy. This suggests that probably both the osteoblasts of osteosarcoma and the stromal cells of giant cell tumor have common origin from the undifferentiated mesenchymal cells of marrow connective tissue. The observation of ultrastructural similarity between the cells of chondrosarcoma, osteogenic sarcoma, and fibrosarcoma also support the concept of their common cells of origin (1, 4, 12).

The histogenesis of the giant cells and the giant cell tumor is currently considered to be from the undifferentiated mesenchymal cells (9). Our finding of malignant cells at three levels of differentiation, such as mononuclear spindle cells, giant cells and the intermediate type cells supports that concept.

The presence of centrioles both at the periphery of giant cell cytoplasm and at the cell center further indicates that the giant cells have arisen as a result of fusion of mononuclear cells, in this case, from the principal stromal spindle cells (8).

The significance of the presence of cell junction in mesenchymal cells like the stromal cells and the giant cells is not understood. It has been also described by Steiner et al (10).

Calcification of the osteoid, a feature so uniform in osteogenic sarcomas, was not seen in any degree in the osteosarcoma component of this tumor (12). This suggests that either the osteoid is incapable of undergoing calcification or that the osteoid and the osteosarcoma component are newcomers in this tumor.

While considering the differential diagnosis, we felt that some of the clinical, gross and light microscopic features of this tumor are similar to what has been described as telangiectatic osteogenic sarcoma by Matsuno et al (5). However, the evidences, being supported by ultrastructural studies, rule out that diagnosis.

The association between growth and osteogenic sarcoma has been well documented. The incidence of osteosarcoma has been clearly correlated with growth spurts and stature in men and women (2). McMaster et al demonstrated increased growth hormone-like activity in the sera of patients with this tumor (7). It is now known that syncytiotrophoblasts of the human placenta secrete human chorionic somatotrophin which has close chemical, structural and physiological similarities to the human growth hormone (11). It is, therefore, possible that this patient's associated pregnancy might have been a factor in the transformation of an otherwise malignant giant cell tumor to focal areas of osteogenic sarcoma.

In summary, extensive study of osteogenic sarcomatous areas and malignant giant cell tumor component in a single tumor failed to distinguish the differences between their principal cell components, the malignant osteoblasts and the stromal spindle cells. We, therefore, suggest that in view of clinical, radiologic and ultrastructural data, the osteogenic sarcoma has been a transformation from the malignant giant cell tumor.

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The Spectrum of Central Nervous System Sarcoidosis. A Clinical and Pathologic Study

JENNY S. WAXMAN, M.D. AND JOANNA HOLLENBERG SHER, M.D.

Abstract

A clinicopathologic study of five cases of central nervous system (CNS) sarcoidosis is compared with other reported series of cases in order to illustrate the spectrum of findings in this disease. The features highlighted by our cases are the predominance of young black people, a very high cerebrospinal fluid (CSF) protein in some cases, and absence of clinical systemic manifestations of the disease in patients with severe CNS involvement. Absence of enlarged lymph nodes or other systemic lesions should not rule out serious consideration of diagnosis of CNS sarcoidosis. Appreciation of the variety of clinical presentations, combined with awareness of some salient features of the disease will aid in clinical recognition.

Sarcoidosis of the central nervous system appearing simultaneously with or subsequently to the systemic disease is usually easily diagnosed. However, when the condition is clinically manifested by neurologic features alone, it may present difficult diagnostic problems because of the protean nature of the pathologic process in the nervous system. The following clinical and pathologic study of five cases is presented in an effort to clarify these aspects of diverse clinical presentation and diagnosis.

The incidence of central nervous system (CNS) involvement in sarcoidosis varies from 1% to 5%, as determined on clinical grounds (5, 21). One autopsy study of patients with systemic sarcoidosis showed CNS involvement in three out of 22 patients (14%), only one of them with clinically manifest neurologic disease (21). Ashkenazy described two cases of CNS disease among 20 autopsied cases of sarcoidosis (1). Apparently, postmortem examination is apt to reveal evidence of subclinical CNS involvement, thus explaining the higher incidence in autopsy as compared with clinical series.

Five cases of CNS sarcoid were studied in our neuropathology laboratory from 1960 to 1975. Four were autopsied cases; and in one, the diagnosis was made on a surgical specimen removed from the spinal cord at laminectomy. During the same period, 11,439 autopsies were performed, including 25 cases of systemic sarcoidosis. Thus, in our autopsy series the incidence of CNS involvement by sarcoidosis is 16%.

Case Reports

Case 1

A 26-year-old black man was hospitalized because of progressive numbness and weakness of the lower extremities of two months' duration. Two weeks previously, he was admitted to another hospital because of inability to walk due to a sudden leg weakness, although standing with support was possible. At that time, cerebrospinal fluid (CSF) obtained by lumbar puncture showed 140 leukocytes per ml, glucose 75 mg% and protein 490 mg%. One year before the admission, an enlarged cervical lymph node was noted. Physical examination revealed an asthenic young male in no acute distress. Multiple, enlarged nontender lymph nodes, up to 3 cm in size, were palpated in the cervical, axillary, epitrochlear, and inguinal areas. There was a complete paralysis of both lower extremities, except for minimal movements of the toes. Symmetrical wasting was evident in the calves and distal thighs, but fasciculations were not observed. Marked hypotonia was noted in both lower extremities. A foot drop was present bilaterally. There was weakness of the lower half of both recti abdomini muscles as demonstrated by Bevor's sign. Tendon reflexes were hyperactive in the lower extremities with a slightly greater response on the right. Bilateral sustained ankle clonus was present. Superficial abdominal reflexes were weak in

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From the Department of Pathology, State University of New York, Downstate Medical Center, Brooklyn, N. Y.

Requests for reprints should be sent to Joanna Sher, M.D., Box 25, SUNY, Downstate Medical Center, 450 Clarkson Ave, Brooklyn, N.Y. 11203.

the lower abdomen, and the cremasteric reflex was absent bilaterally. The Babinski sign was absent. There was diminished sensation to pinprick, light touch, temperature, and vibration up to the level of T-12 bilaterally. Cranial nerve and cerebellar functions were normal. Anal sphincter tone was good. The remainder of the physical examination was unremarkable. Skin tests with PPD and histoplasmin were negative. Three gastric aspirates and CSF cultured for acid-fast bacilli yielded no growth. VDRL was negative. Chest x-rays revealed bilateral hilar lymphadenopathy, and diffuse bilateral pulmonary infiltrates. X-rays of the skull, brain scan and electroencephalogram were normal. The lumbar myelogram showed almost complete obstruction at the level of T-12 - L-1. Biopsy of a cervical lymph node revealed multiple nonnecrotizing epitheloid cell granulomas, and the stains for acid-fast bacilli and fungi were negative. The patient was placed on antituberculous therapy, but his neurologic condition worsened; he could no longer move his toes, and he began losing bladder function. Decompressive laminectomy at levels T-8 - L-1 was performed on the 18th hospital day. The operative findings were: "A swollen cord with an area of demarcated abnormal tissue on top of which there was a 3 mm nodule of hard tissue. Under it, at levels T-11 to T-12, the cord was swollen, with an appearance of an intramedullary tumor. There was another 5 mm intramedullary nodule in anterolateral aspect of the cord at the level of T-9 to T-10. No ventral or epidural abnormalities were found, and the medullary cone appeared normal". The abnormal intramedullary and subpial tissues were resected. Pathologic examination revealed masses of chronic inflammatory tissue with multiple epitheloid cell granulomas. Stains for fungi and acid-fast bacilli were negative. Following the operation there was a gradual and eventually full recovery from the paralysis.

Case 2

A 15-year-old black male was hospitalized because of episodes of headaches and vomiting of five weeks' duration. He became dizzy, confused and disoriented one day prior to admission. His past history was unremarkable except for seizures in infancy. On physical examination he was found alert, oriented, afebrile, and there were no abnormal findings. Detailed neurologic examination was also normal. The CSF showed an opening pressure of 120 mm water, protein over 360 mg%, and glucose 75, 30 and 50 mg%. All cultures were negative. Electroencephalogram (EEG) was focally abnormal, with a possible lesion in or near the right posterior quadrant. X-rays of the skull and chest were normal. Pneumoencephalogram (PEG) showed evidence of a communicating hydrocephalus. The patient left the hospital and was free of symptoms until his second admission 18 months later when he was hospitalized because of seizures and intermittent "decerebrate posturing." A chest x-ray, left carotid angiogram and PEG were all reported as normal this time. The EEG showed excessive bianterior thete and bifrontal delta waves. CSF cultures were negative. The CSF opening pressure was 260 mm water, protein 335 mg%, with gamma globulin over 24 mg%, there were 3 cells per ml. The patient was discharged after one month of hospitalization with antiseizure medication. He remained well for five months, and was then hospitalized again because of headaches, vomiting, gait disturbances, and hallucinations. Examination showed nystagmus to the right and a tendency to fall to the left. The finger to nose test was impaired bilaterally. The CSF showed 234 leukocytes per ml (no malignant cells were found), protein 780 mg%, and glucose 45 mg%. PEG showed no filling of the ventricles. Left carotid angiogram showed an elevation of the left anterior cerebral artery. On ventriculogram, air and contrast material failed to enter the third ventricle from either dilated lateral ventricle. Bilateral ventriculoperitoneal shunts were placed, after which the patient's mental status and gait improved dramatically. Subsequent recurrent staphylococcal infections necessitated several changes of the shunt. The patient's neurological status declined progressively and he eventually expired two and a half years after the onset of symptoms.

Case 3

A 43-year-old black man was hospitalized because of sudden loss of consciousness, and seizures. On admission the blood pressure was 200/140 mm Hg. He responded only to painful stimuli. The pupils were equal, fixed, and dilated. There was slight blurring of the left optic disc. Babinski sign was present bilaterally. The CSF was bloody, with the opening pressure over 300 mm water. The patient expired eight hours after admission.

Case 4

A 50-year-old black man was in apparent good health until two years prior to his final admission, when he was investigated for bilateral flank pain. Kidney stones were found. He was treated conservatively, with several subsequent hospitalizations. His last admission was also because of hematuria and flank pain accompanied by severe shortness of breath and weakness. On admission, the blood pressure 180/100 mm Hg and the pulse, 98 per minute. He was breathing rapidly and with difficulty. Bilateral costovertebral angle tenderness was present. Blood chemistry determinations showed calcium of 12.4 mg%, phosphorus 7.8 mg%, uric acid 13.8 mg% and blood urea nitrogen 180 mg%. On the fifth hospital day he collapsed while sitting in a chair, and never regained consciousness. He expired several days later.

Case 5

A 29-year-old black woman was hospitalized elsewhere because of paraplegia and bitemporal headache. Lumbar puncture showed an opening pressure of 500 mm water, protein 230 mg% and 90 lymphocytes per ml. She was found to have diabetes, and was treated initially with insulin. A diagnosis of chronic lymphocytic choriomeningitis was made. Following discharge, the patient remained paraplegic. Fifteen months later she became blind and was said to have psychiatric disturbances (nervousness, insomnia, memory loss, and hallucinations). Amenorrhea was noted. She was hospitalized at our institution three years after her initial neurologic manifestations, because of nausea, vomiting, headache, inability to speak, and incoordination, followed by complete unresponsiveness. On physical examination her temperature was 103° F, blood pressure 110/80 mm Hg, and pulse, 110 per minute. She was comatose, responding only to deep stimuli. The pupils were dilated and not reactive to light. Corneal reflexes were absent. Fundi showed optic atrophy. Babinski sign was present bilaterally. The CSF was clear and showed an opening pressure of 150 mm water, protein 1,145 mg%, 110 white blood cells per ml (80% lymphocytes), and glucose 75 mg%. Blood glucose was 148 mg%. Cardiac arrest occurred one hour after the admission, but was successfully treated. Brain scan suggested a lesion in the right hemisphere. Echoencephalogram showed no shift of the midline. Repeat lumbar puncture showed clear fluid with 200 red blood cells and 210 leukocytes per ml (80% lymphocytes), protein 335 mg% and glucose 165 mg% (blood glucose 195 mg%). Right carotid angiogram was normal. Subsequently CPK rose to 520, SGOT to 600, and LDH to 1,100 IU. The patient expired after a week of hospitalization.

Discussion

A. Clinical Manifestations

1. Age, Sex, Race, and Course: The clinical features of our cases are summarized in Table I. Certain characteristic clinical features are apparent in this group of cases. All the patients were black and relatively young (18 to 50 years of age). A recent review of several large series of cases shows that the majority of patients were under 40 years of age when the disease began, and that in New York and Los Angeles, the majority of patients with sarcoidosis were black(23). Ricker and Clark in a study of 271 cases that occurred among military personnel, also showed preponderance of black patients with this disease (21). Although the majority of patients with CNS sarcoidosis are young adults, sarcoid granulomas in the CNS have been found in a three-month-old infant with clinical meningitis, and in a 66-year-old woman with a mass in the midcervical spinal cord (12, 17). Four of our five patients were males, although generally sarcoidosis equally affects both sexes (23). The clinical course, measurable in four of our five patients, was prolonged, over one to three years. This is analogous to the observations of other authors, who have recorded clinical course in patients with CNS sarcoid of up to 10 years (1, 2, 10, 12, 16). The course has been described as either remittent, some remissions lasting for years, or as relentlessly progressive. In our group of cases, the patient with hydrocephalus (Case 2) illustrates a remittent course with several periods of four to five months of relative

TABLE I

Clinical and Pathologic Findings in Five Cases of CNS Sarcoidosis

	Age/Sex/Race	Symptoms	Duration of course	Clinical diagnosis	Clinicopathologic correlation
Case 1	26/male/black	paraplegia lymphadenopathy	1 year	sarcoidosis	intramedullary granulomas, T9-12. Noncaseating granulomas in cervical nodes
Case 2	18/male/black	headaches, vomiting, seizures, ataxia	3 years	hydrocephalus	granulomatous meningitis and ependymitis, with obstruction of foramina of Monroe and Luschka
Case 3	43/male/black	none	—	—	Incidental (asymptomatic) granulomas of meninges. Patient died of hypertensive cerebral hemorrhage.
Case 4	50/male/black	flank pain hematuria	2 years	nephrolithiasis chronic pyelonephritis uremia	hypercalcemia, asymptomatic granulomas of basal meninges
Case 5	29/female/black	paraplegia blindness amenorrhea memory loss and hallucinations.	3 years	lymphocytic choriomeningitis	extensive granulomatosis, hypothalamus and optic nerves and chiasm. Granulomatous meningitis and radiculoneuritis, brain and spinal cord.

freedom from the symptoms. On the other hand, the course of the young women with hypothalamic–optic chiasm disease (Case 5)–was progressive, as well as prolonged.

It is sometimes said that no clinical syndrome is characteristic of sarcoidosis of the CNS, and that diversity of clinical signs and symptoms is the rule (3, 5, 6, 12). Our cases illustrate four main types of clinical symptoms (Table I). Paraplegia, secondary to granulomas of the spinal cord, was seen in two instances. Symptoms of hydrocephalus secondary to granulomatous ependymitis and meningitis is illustrated by Case 2. Symptoms of optic nerve and hypothalamic involvement by granulomas occurred in Case 5. In two cases there were no symptoms referrable to extensive granulomatous meningitis.

2. Paraplegia: In general, the spinal cord is rarely involved in sarcoidosis. In a series of 907 patients with sarcoidosis, 5% of whom had neurologic findings, only one patient had a paraparesis because of cord compression by arachnoidal sarcoid granulomas (29). Only 11 cases of proven spinal cord sarcoidosis have been reported (18). One such case was a 36-year-old black woman diagnosed clinically as having an intramedullary tumor, which proved on pathologic examination to be a granulomatous lesion (2). The patient's paraplegia improved remarkably on steroid treatment. Most patients with spinal sarcoidosis have paraplegia, bladder and bowel dysfunction and a sensory deficit level, findings identical to those caused by neoplasms within the spinal canal. The disease is often characterized by remissions and exacerbations, multiplicity of lesions, and self-limiting nature because of spontaneous healing. Usually patients with symptoms referrable to the spinal cord do not have primary intramedullary lesions, but show cord compression secondary to meningeal granulomas

3. Hydrocephalus: Although granulomatous arachnoiditis is a common component of CNS sarcoid, hydrocephalus is a relatively rare occurrence. In a review of 118 cases of CNS sarcoidosis, Colover described three cases of hydrocephalus, all secondary to leptomengitis (4). Hydrocephalus with ependymitis and choroiditis is apparently very unusual. One such case has been reported, of a 31-year-old man who had symptoms of increased intracranial pressure in association with Meniere's syndrome, trigeminal neuralgia, and deafness (15).

Visual and Hypothalamic Symptoms: Optic-hypothalamic dysfunction is one of the most common types of clinical symptoms of CNS sarcoidosis. Its most frequent form includes symptoms of diabetes insipidus (DI). More than 60 cases of definite DI associated with sarcoidosis have been reported since 1909 (30). In 1935, Tillgreen presented the first patient with DI in whom a clinical diagnosis of pituitary sarcoidosis was confirmed histologically (26). Colover in a review of 118 cases of CNS sarcoidosis observed that 17% of them had evidence of DI (4). Pennell concluded that DI was the most common manifestation of sarcoidosis of the CNS, occurring in 35% of reported cases (19). It is generally appreciated that the lesions of cerebral sarcoidosis involve the structures at the base of the brain, including the meninges, floor of the third ventricle, optic nerves, and pituitary. The symptoms of this form may be polydypsia and polyuria alone, or combined with visual disturbances, or with other manifestations of hypothalamic-pituitary disease, such as hyperthermia, somnolence, impotence or amenorrhea. Hypopituitarism is much less commonly reported than DI, although the selective tendency of sarcoidosis to infiltrate both the hypothalamus and the pituitary stalk leads one to suspect that a mild hypopituitarism may occur more often than it has been reported. This problem was investigated by Jefferson, who found DI in a total of 14 cases, and evidence of deficiency of one or more anterior pituitary hormones in 17 cases altogether (12). It is noteworthy that although Case 5 had extensive pituitary and hypothalamic destruction by sarcoidosis, DI was nor apparent. Conversely, evidence of partial hypopituitarism, as manifested by amenorrhea, was a prominent early finding. The improvement in this patient's diabetes mellitus, as shown by decreased insulin requirement, was also probably a clinical manifestation of extensive pituitary destruction.

5. Asymptomatic Cases: Clinically silent CNS sarcoidosis is perhaps the most common form. In our registry, two cases out of 25 showed no clinical manifestations referrable to extensive meningeal involvement. Although it is usually stated that neurologic symptoms are frequently among the first to indicate the presence of the disease, it is not uncommon for CNS sarcoidosis to be unsuspected and only accidentally discovered at autopsy. Since there may be CNS involvement of a degree not sufficient to disturb the function of the nervous system, it is not surprising that in some cases the diagnosis is possible only at autopsy. Ricker and Clark, in their autopsy series of 22 cases of sarcoidosis, described 14 (66.6%) patients in whom the CNS involvement had been clinically unsuspected (21).

6. Neuritis: Other types of clinical symptoms reported in CNS sarcoid were not manifested in our group of cases. We had no case of clinically evident peripheral or cranial neuritis, other than optic, although pathologic involvement of cranial and spinal nerve roots was present in Case 5. However, it is apparent from analyzing the literature on CNS sarcoidosis that the most common lesions are in the cranial and peripheral nerves. The symptoms of peripheral neuropathy, localized or widespread, may succeed, accompany, or precede cranial nerve lesions. Intercostal neuritis with sensory loss and corresponding loss of abdominal reflexes was described by many early authors (7, 11, 20, 28). Hypalgesia in glove and stocking distribution, as well as loss of vibration sense and sensory ataxia may also occur (25). Facial paralysis, unilateral or bilateral, is often the first indication of disease, occurring in about 50% of patients with nervous system involvement. It may occur in the absence of parotitis and may be associated with disturbances of taste (4, 8). Heerfordt's syndrome (cranial and peripheral neuropathy, uveoparotitis, and diabetes insipidus) is a recognized constellation of symptoms in sarcoidosis (12). Compression of the third cranial nerve may also be expressed in symptoms of ophtalmoplegia and sluggishness of pupillary responses (4). Trigeminal nerve impairment, nerve deafness, disturbances of vestibular function, and fibrillation of the tongue, have all been ascribed to the cranial neuritis of sarcoidosis (4, 14, 20). It is not always possible to find pathologic evidence at autopsy for the cranial or peripheral nerve dysfunction, since many peripheral nerve lesions may improve spontaneously, as occurs in the systemic granulomas.

7. *Mass Effect:* Occasionally, sarcoid granulomas form large masses, resulting in clinical symptoms suggestive of a CNS neoplasm. In our cases with paraplegia, the spinal cord granulomas acted as tumor masses in producing clinical symptoms. None of our cases showed a large enough intracerebral mass to produce tumor-like symptoms. This rare event has been reported only 12 times (10).

8. *Mental Dysfunction:* It is noteworthy that seizures and hallucinations were prominent clinical features in two of our cases, and that one patient had severe memory loss with signs of organic psychosis (Case 5). Hallucinations are described as occurring occasionally during the course of the disease but not as an initial symptom (16). Pure organic psychosis has not been described as a symptom of CNS sarcoidosis but has been associated with generalized brain dysfunction.

B. Laboratory Findings

1. *CSF:* The pertinent laboratory data in our cases are summarized in Table II. High CSF protein with levels over 1 gm% was a consistent finding in our cases. Other series, however, show some cases with normal CSF protein levels (2, 9). Cells in the CSF were increased in all cases, because of the chronic meningitis. Glucose levels were variable and were somewhat low only in Case 2, where chronic fibrosing meningitis and ependymitis were present. A majority of the authors report normal CSF sugar levels, but low values in range of 30 mg% have been reported occasionally (4, 7, 9).

2. *Serum Calcium:* Elevated serum calcium is not an uncommon feature of sarcoidosis, and it was noted in one of our patients whose CNS involvement was clinically silent. Even with extensive CNS involvement, the serum calcium can remain normal. About 13% of patients with systemic sarcoidosis show elevated serum calcium, varying from 7% to 24% in different series (23). Efforts to define features that distinguish patients in whom hypercalcemia will develop from other patients with sarcoid have not been fruitful. Labow found hypercalcemia more often in blacks, while Taylor reported opposite results (13, 24). Scholz, in 1959, remarked that a male with saroidosis has an apparent predilection for hypercalcemia and renal impairment, and this view has been supported by others (22). One large study reported hypercalcemia in 18.6% of the males, but in only 13.7% of the females (30). There is no direct correlation between organ involvement and calcium level in the blood, since not every patient with osseous sarcoid has hypercalcemia. Labow has observed the more frequent occurrence of hypercalcemia in patients with pulmonary sarcoidosis, and this view is in agreement with the general opinion that hypercalcemia is more frequent in patients with widely disseminated disease (13).

C. Pathology

The pathologic findings in our cases are summarized in Table III. The constant pathologic finding in the CNS of our five cases was the presence of typical sarcoid granulomas in the cerebrospinal meninges and in the parenchyma of the brain and spinal cord. These granulomas consisted of polyhedral epithelioid cells, with a tendency to a concentric arrangement, with lymphocytes, monocytes, fibroblasts and giant cells. They were nonnecrotizing, and stains for acid-fast bacilli were negative. Many lesions showed varying degrees of fibrosis, hyalinization, and replacement by scar tissue, with only a few compressed epitheloid cells, a small cluster of lymphocytes, or an isolated giant cell. These old lesions were

TABLE II

Cerebrospinal Fluid (CSF) Data and Serum Calcium in Five Cases of CNS Sarcoidosis

	CSF Data				
	pressure (mm. H_2O)	protein (mg%)	cells/ml	glucose (mg%)	serum calcium (mg%)
Case 1	—	490	140	75	8.1
Case 2	120–260	355–780	3–234	30–75	9.1–10.8
Case 3	63	300	—	—	—
Case 4	—	—	—	—	12.4
Case 5	150–500	230–1145	90–210 (80% lymphs)	165	10

TABLE III

Pathologic Findings in Five Cases of CNS Sarcoidosis

	Systemic Granulomas							CNS
	lymph nodes	lung	spleen	liver	kidney	muscle	myocardium	
Case 1	cervical	—	—	—	—	—	—	subpial and intramedullary granulomas T9-12
Case 2	paratracheal	+	+	—	—	—	—	granulomatous meningitis and ependymitis, with obstruction o foramina of Monroe and fourth ventricle
Case 3	paratracheal	+	+	+	+	—	+	granulomas of meninges, brain and spinal cord
Case 4	hilar and peripancreatic	+	+	—	—	—	—	multiple, noncaseating granulomas of basal meninges
Case 5	mediastinal	+	—	+	—	—	—	Extensive chronic granulomatous meningitis and radiculoneuritis, brain and spinal cord. Granulomatosis hypothalamu and optic nerves and chiasm. Granulomas of cerebral cortex basal ganglia and brain stem, ependymitis of fourth ventricle

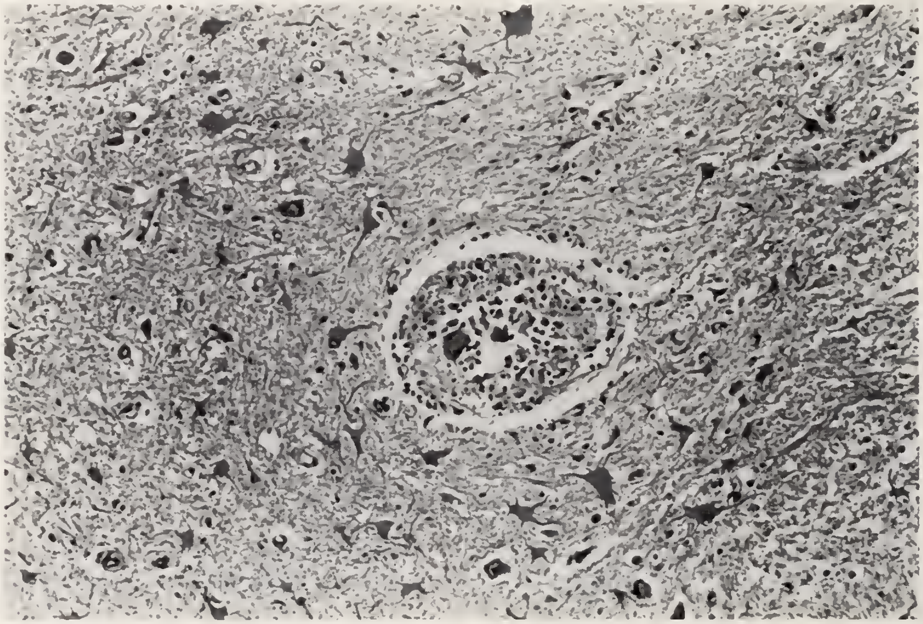

FIG. 1. Microscopic view of anterior horn of spinal cord, showing small granuloma surrounded by reactive astrocytes and motor neuron Hematoxylin and eosin, × 500.

occasionally seen side by side with active granulomas. An unequivocal, completely healed meningovascular sarcoidosis has not yet been described (27). All cases revealed the tendency of the granulomatous inflammation to occur in perivascular areas in the meninges, as well as in the brain substance, along the perivascular spaces of the perforating vessels. The intracerebral regions showing the most severe involvement were hypothalamus and brain stem (Cases 2 and 5). The spinal cord involvement was present in one surgical specimen, and leptomeningeal involvement, in one of the autopsied cases (Fig. 1). Anterior horn granulomas were also seen in these two cases. In two cases there was a marked aggregation of granulomas in the subependymal layer of the ventricular system accompanied by disruption of the ependyma and proliferation of the subependymal glia. This was observed mostly around the fourth ventricle and in one case i produced occlusion of the foramina of Luschka and Monroe, causing narrowing of the aqueduct and leading t hydrocephalus. Fibrosis of the meninges also contribute to the development of the hydrocephalus. Aggregation of granulomas forming tumor-like masses replacing th hypothalamus, the optic chiasm, and the optic nerve ar illustrated in Case 5 (Figs. 2 and 3). Granulomatou inflammation of the seventh cranial nerve, seen in Cas 5, is shown in Figure 4.

D. Differential Diagnosis

It is not surprising that CNS sarcoidosis may simulat other neurological conditions. Because of its spontaneou remissions and exacerbations, multiple sclerosis is one o the diseases with which it may be confused clinically. Tuberculous meningitis may be similar in its clinical symptomatology. Although in the latter the low CSF sugar may be helpful, culture of the CSF is the only definite way to make the clinical distinction. Pathologically, while both tuberculosis and sarcoid have a definite tendency to involve the basal meninges, direct massive invasion of the brain from the subarachnoid space is seen much more frequently in the sarcoidosis. Vasculitis is a common feature of tuberculous meningitis, whereas the inflammation in sarcoidosis is clearly perivascular. Sarcoidosis may mimic cerebral or spinal tumors. As has been shown, it may appear as a personality disorder, or as an endocrine dysfunction (hypopituitarism).

The diagnosis of sarcoidosis was made clinically in only one of our cases (Case 1). Other autopsy series of CNS sarcoid also show failure of clinical diagnosis in about 33-64% of cases (21). Although all of our five cases

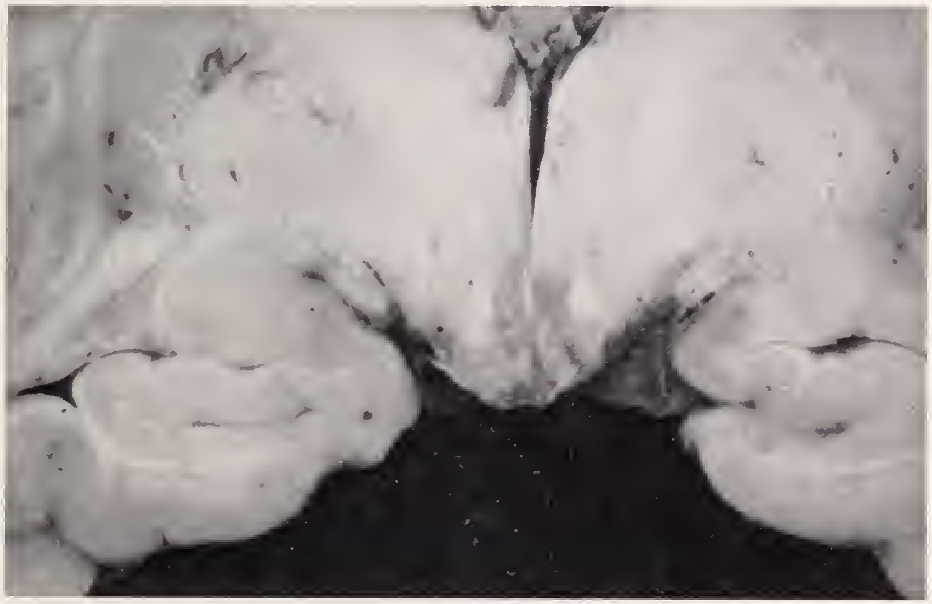

Fig. 2. Cross-section through hypothalamus and third ventricle, showing tumorlike granulomatous masses replacing the median eminence.

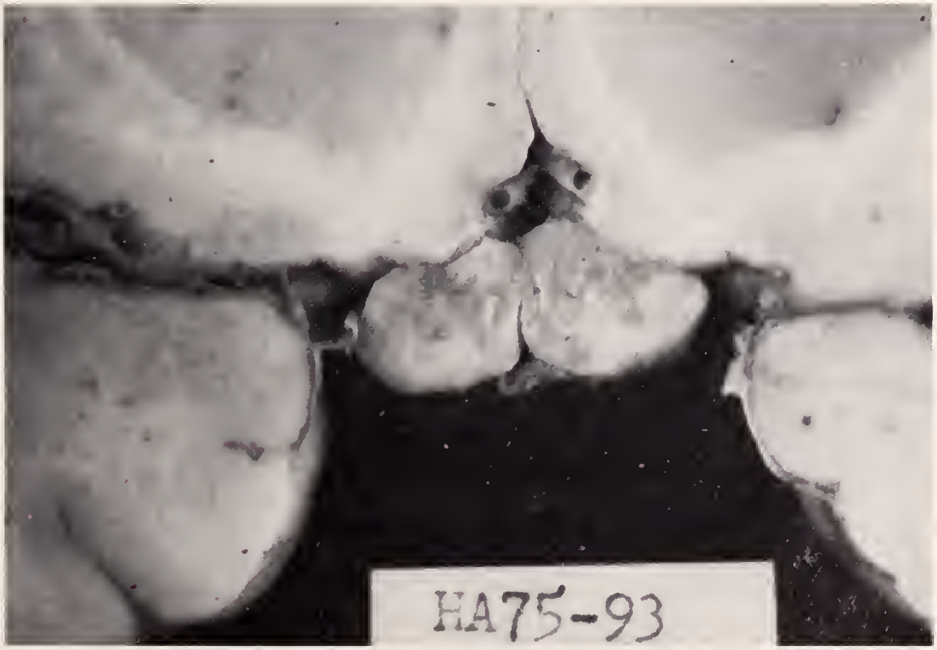

Fig. 3. Cross-section through inferior frontal lobes, temporal poles, and optic nerves, showing marked enlargement of the optic nerves due to ranulomatous inflammation.

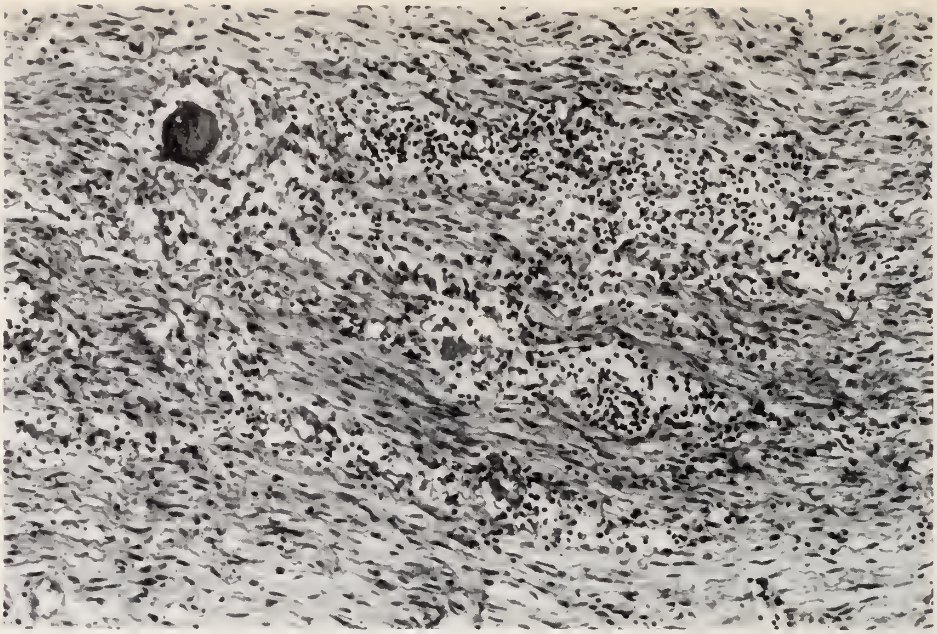

FIG. 4. Microscopic view of facial nerve showing extensive chronic inflammatory infiltrate and giant cell. Hematoxylin and eosin, × 500.

showed systemic involvement by sarcoidosis at autopsy (Table III), only one had clinical evidence of this involvement. Clinically, patients with systemic sarcoidosis can have only CNS symptomatology despite involvement of other organs (5, 12, 27). Ashkenazy has stated that extracranial lesions are nearly always present, but may be clinically silent (1). In only two out of 13 cases in his series, the disease involved CNS exclusively (1). In our cases, careful pathologic examination showed granulomas in lymph nodes in all cases, and in the lungs of four out of the five cases. Spleen, liver, and kidney were less often involved. These findings suggest that biopsy of lymph nodes or lung may be useful in finding clinically elusive granulomatous disease.

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Self-induced Transient Ischemic Attack in a Physician Demonstrating Carotid Massage

WILLIAM B. COHEN, M.D. AND JULIUS H. JACOBSON II, M.D.

Introduction

Transient ischemic attack provoked by carotid massage or compression has been reported several times in the literature. Aside from their value as a warning, these cases have also provided important evidence in favor of an embolic pathogenesis for the evolution of stroke (4). In a time when carotid compression is a common practice in vascular laboratories, it is timely to describe another such case with an unusual presentation.

Case Report

Dr. G. is a 50-year-old practicing internist in New York who has no history of diabetes, hypertension, smoking hyperlipidemia, hypercholesterolemia, neurologic symptoms, angina or intermittent claudication. He was in the midst of a heavy office schedule one morning last year, and specifically was instructing a young female patient how to deal with her frequent attacks of paroxysmal atrial tachycardia. As part of his demonstration he very gently massaged the area of his own left carotid bifurcation. The doctor was talking to his patient while he did this and reported that he instantaneously lost the ability to articulate, though he knew precisely what he wanted to say. His patient claimed that he became blanched and diaphoretic. Concurrent with the motor aphasia he developed paresis of the right arm and hand, and numbness of the hand. In approximately five seconds he could speak normally again, but the paresis remained throughout his office hours which were completed as scheduled. When seen by a neurologist later in the day, his only abnormality was weakness of the hand. Forty-eight hours, after the incident symptoms and signs had disappeared. Dr. G. was admitted to the hospital where carotid angiography was performed. In the A-P projection of th left carotid bifurcation no lesion was demonstrated; however, in the lateral projection anulcerated plaque wa seen (Fig. 1). He underwent left carotid endarterectomy

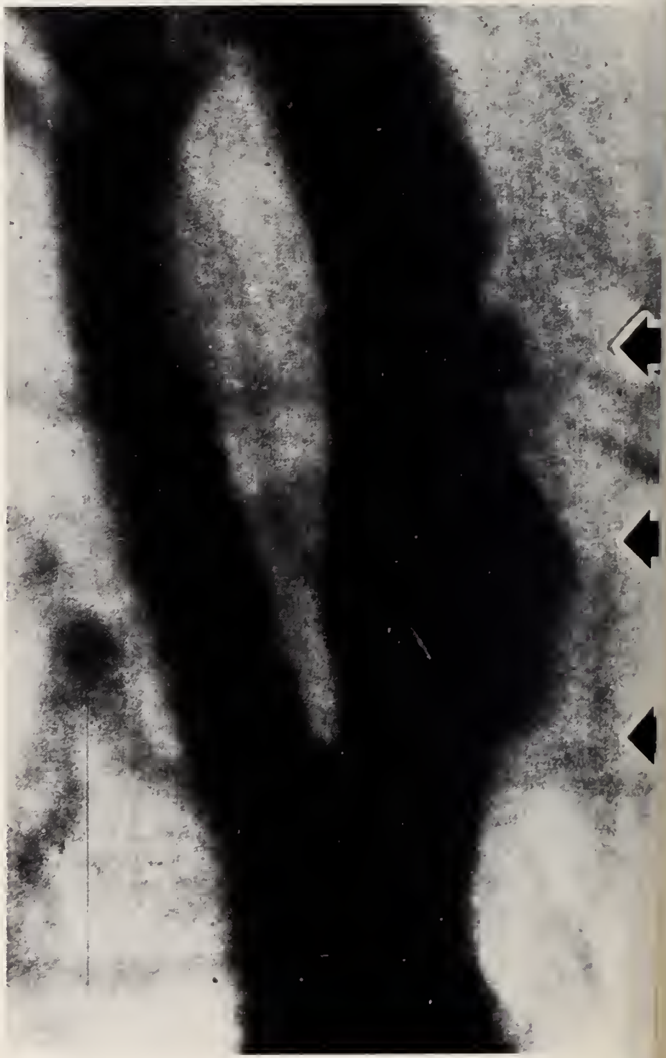

Fig. 1. Detail of subtraction arteriogram demonstrating ulcerati of the internal carotid artery. At surgery a nonadherent clot filled t concavity of the ulcerated area.

From the Department of Surgery, Division of Vascular Surgery, Mount Sinai School of Medicine, CUNY, New York, N.Y. 10029.

Requests for reprints should be sent to Dr. Julius Jacobson II, 1176 Fifth Avenue, New York, N.Y. 10029.

When the arteriotomy was made, a large posterior ulcerated plaque was noted that contained loose fibrinous material. His recovery was uneventful and seven months later he had no further episodes and is back to active practice.

Discussion

In 1941, it was first recorded that irreversible neurologic damage could result from carotid manipulation but it was not until 1946 that Askey presented four cases that seemed to be caused by embolization from the ipsilateral carotid (1). In 1961, Calverly and Millikan presented three additional cases where gentle carotid palpation resulted in sudden contralateral hemiparesis (3). It was partly on the basis of these cases that Millikan in 1965 developed an embolic theory for the pathogenesis of TIA; at the same time, he described three more patients suffering contralateral paresis after carotid massage (4). Even the most gentle carotid manipulation may result in embolization from a plaque. Bergan has stated that during very gentle dissection of the carotid bifurcation, ophthalmologists at his institution observed emboli passing through the retinal circulation (2).

This case is important because it reminds those who practice carotid compression during the Doppler Ophthalmic examination and those who use carotid massage, that there may be catastrophic complications from these maneuvers; this has been shown to be true in a relatively young individual with no history of occlusive disease. It reemphasizes the need for cautious dissection of the carotid bifurcation during carotid endarterectomy. And finally, the arteriogram demonstrates once again, that obtaining only one view in carotid angiography is inadequate.

Summary

A practicing physician with no antecedent history indicating arteriosclerotic occlusive disease has had a TIA while demonstrating carotid massage. The importance of this case and similar cases are discussed.

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Syphilitic Osteomyelitis with Diffusely Abnormal Bone Scan

DAVID SIEGEL, M.D. AND SHALOM Z. HIRSCHMAN, M.D.

Abstract

A case of early syphilis in which osteomyelitis was the major clinical manifestation is presented. Technetium 99m bone scan showed multiple areas of increased uptake, including areas corresponding to abnormal bones detected on routine skeletal roentge survey. The patient responded symptomatically to intramuscular procaine penicillin.

Introduction

Osseous disease is a well-recognized complication of late or congenital syphilis (1). In the former, gummas are formed in response to the presence of blood-borne treponemes; while in the latter, the characteristic lesion of the first six months of life is osteochondritis. In contrast, bone lesions infrequently are observed in early syphilis. In a series of 10,000 cases of early syphilis gathered over a 22-year period, only 15 instances of destructive bone lesions were seen (2). Osteoperiostitis is the most common lesion, followed by osteitis and osteomyelitis.

It may be difficult to differentiate early osseous syphilis from more common entities involving bone, such as pyogenic, fungal or tuberculous osteomyelitis, and multiple myeloma, or other malignant processes. We report a case of early syphilis in which osteomyelitis was the major clinical manifestation. The microscopic pathology, roentgenologic appearance and characteristics of the technetium 99m scans of the involved bones are described

Case Report

A 31-year-old Ethiopian male was admitted to The Mount Sinai Hospital complaining of pretibial pain of six weeks' duration in the right leg. Six months before admission, he had noted a painless lesion on the shaft of his penis. He took eight tetracycline capsules and the lesion resolved. Six weeks before admission, the patient experienced mild pain in his right lower extremity that increased in intensity over the ensuing weeks. The pain was relieved with activity and was worse at night. Four weeks later, he came to the United States from Addis Ababa, Ethiopia and was referred to The Mount Sina Hospital. During the preceeding month, the patient had a weight loss of 20 pounds and frequent night sweats There was no history of skin rash, tuberculosis, trauma to the leg, or animal exposure. The patient reported multiple heterosexual contacts during the past year.

Physical examination revealed an alert, intelligent yound man. Vital signs were normal. There was no skin rash or peripheral adenopathy. The remainder of the physical examination was unremarkable except for an area of hypopigmentation on the shaft of the penis.

Laboratory data included an erythrocyte sedimentation rate (ESR) of 120mm/hr (Westergren), hemoglobin of 12.1gm/100ml, and white blood cell count (WBC) o 5,400/mm^3, with 74 neutrophils, six band forms, 11 lymphocytes, six monocytes and one basophil. Serum alkaline phosphatase was 238 IU/L (normal, 30–90); the remainder of the SMA-12 was normal. Latex fixation and antinuclear antibody tests were negative. VDRL and treponemal hemagglutination titers were 1:64 and >1 2560, respectively. A skeletal roentgen survey showed a diffuse, destructive pattern with periosteal reaction involving both femurs and the right fibula and tibia as well as the left humerus (Fig. 1). Lytic areas of the lower ribs were also noted. A technetium 99m bone scan showed increased activity in the right shoulder, left scapula upper half of the right humerus, right clavicle, right and left femurs, right tibia, and multiple ribs bilaterally (Fig 2). Lumbar puncture and liver scan were normal.

Under general anesthesia, an open bone biopsy of the right fibula was performed. An inflammatory infiltrate consisting on neutrophilic leukocytes, histiocytes, lymphocytes, and fibroblasts was present (Fig. 3). Gram

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From the Division of Infectious Diseases, Department of Medicine, Mount Sinai School of Medicine of The City University of New York, New York, N.Y. 10029.

Requests for reprints should be sent to Dr. Shalom Z. Hirschman, Division of Infectious Diseases, The Mount Sinai Hospital, Fifth Avenue and 100th Street, New York, N.Y. 10029.

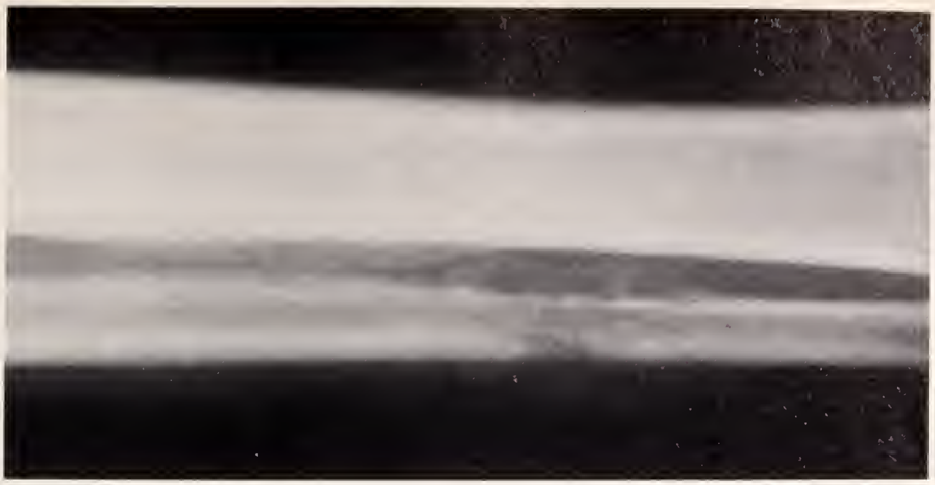

FIG. 1. Roentgenogram of right tibia and fibula showing lytic areas, periosteal elevation, and soft tissue swelling.

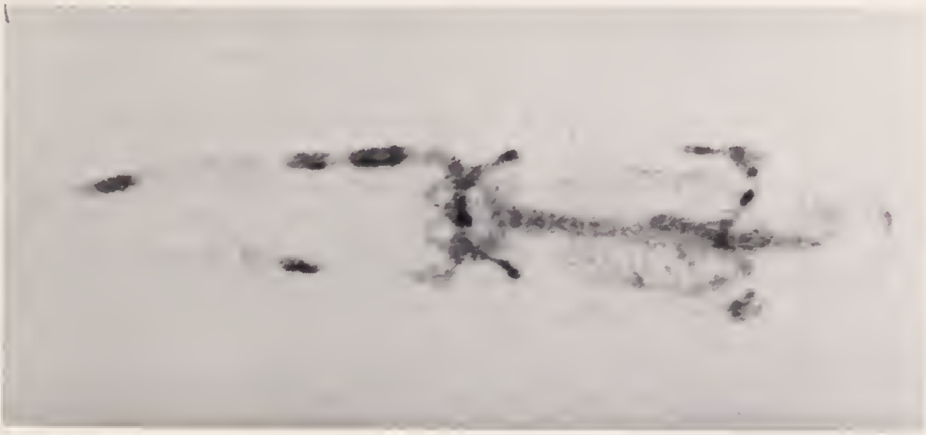

FIG. 2. Technetium 99m bone scan before treatment showing increased uptake of radionuclide in the right shoulder, humerus, clavical, and ibia, the left scapula, right and left femurs, and in multiple ribs bilaterally. Repeat technetium 99m bone scan one month after penicillin therapy was unchanged.

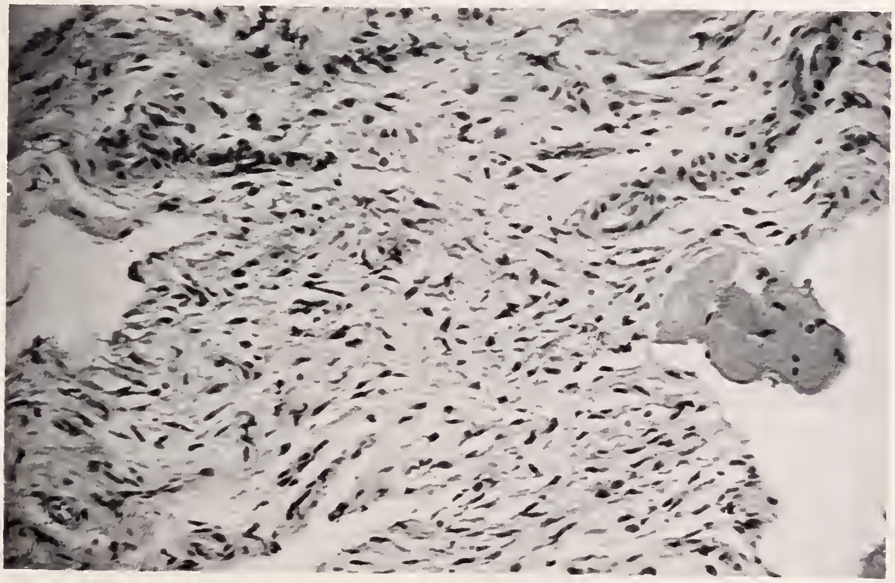

FIG. 3. Bone biopsy of right fibula showing an inflammatory infiltrate containing neutrophils, histiocytes, lymphocytes and fibroblasts. hematoxylin and eosin stain; original magnification, X40).

fungal, and acid-fast stains and cultures were negative. Direct dark field examination and special stains for treponemes were unremarkable.

The patient was treated with procaine penicillin, 600,000 units intramuscularly twice daily for ten days. One day after beginning therapy, there was marked decrease in leg pain. When seen one month after completing treatment, the patient had gained weight, had no bone pain or night sweats, and had been able to return to a normal level of activity. A repeat bone scan was unchanged from the previous examination.

Discussion

The history of a chancre, the markedly positive serologic tests, and the dramatic response to penicillin therapy established the diagnosis of secondary syphilis in this patient. Worsening of bone pain at night and its improvement with activity is characteristic of so-called osteocopic syphilitic bone pain (2). The lack of cutaneous and muscocal lesions and the absence of generalized adenopathy are unusual in secondary lues but these manifestations are not present in all cases (2). When bone biopsies have been done, they have rarely demonstrated spirochetes in the lesion (3). Bone lesions are usually characterized by round cell infiltration (2).

The true incidence of bony involvement in early syphilis is unknown. In one early study, 165 patients with primary and secondary syphilis were examined for objective evidence of skeletal abnormalities and evidence of bone or joint involvement was found in 60, or 36% of the total (4). Roentgenologic studies were not done and, thus, no true indication of the frequency of destructive bony lesions can be made. In a later study, routine skull roentgenograms were performed on 80 consecutive patients with secondary syphilis (5). Demonstrable skull lesions were found in seven patients, or 8.7%. The skull followed by the sternoclavicular region and the long bones of the lower extremities are the most common bones involved in secondary syphilis (2).

The abnormalities seen on roentgenograms in our patient are characteristic of the bone lesions seen in early syphilis. Swelling of soft tissue or hazy periosteal markings parallel to the surface of the bone are indicative of periostitis. Medullary involvement is indicated when the osteolytic process involves the inner portion of the cortex. Skull lesions are characterized by irregular circular areas of decreased density of varying size, with a porous and wormeaten appearance (5). This picture is differentiated from gummatous osteomyelitis seen in late syphilis where, in addition to destruction of bone, there is usually evidence of bone proliferation giving rise to exostoses and periosteal thickening.

Defects in spongy (trabecular) bone must be approximately 1.5 cm in diameter, and 50% to 75% of the calcium salts must be lost, before a lesion is visible on roentgenogram (6). Radionuclides used in bone scanning, such as technetium 99m, will accumulate in bone lesions long before significant bony decalcification has occurred and are, thus, a sensitive indicator of metastatic bone disease and other bone pathology. The bone scan in our patient detected bony disease both in areas found to be abnormal and normal on the skeletal roentgen survey. It is likely that if the patient had been left untreated, all abnormal areas on the bone scan would eventually have shown abnormalities on routine roentgen examination. The lack of resolution of abnormalities seen on the bone scan one month after treatment is similar to the slow healing of syphilitic bone lesions on routine roentgens, where up to ten months may be necessary for complete healing of bone lesions (7).

Optimal therapy for early syphilitic bone lesions is unknown. Recent reports have noted good responses to both procaine penicillin G, 1.2 million units intramuscularly daily for ten days and to the combination of a single intramuscular dose of 3.0 million units of benzathine penicillin G and procaine penicillin G, 600,000 units intramuscularly daily for ten days (3, 8). Our patient has a good response to 1.2 million units of procaine penicillin G given intramuscularly daily for ten days.

The report of this case should alert clinicians to the possible diagnosis of syphilis in the patient with bone pain and diffusely abnormal bone scan.

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Simulated Outflow Capacity in Vascular Reconstruction: A Preliminary Report

VICTOR BAUM, M.D., F.A.C.S., ARIEH KAYNAN, M.D., AND PINKUS H. SZUCHMACHER, M.D., F.A.C.S.

The importance of a patent outflow tract (runoff) in the surgical relief of arterial obstruction has long been recognized (1). This traditionally has been estimated by arteriography, distal arterial pressure measurements, direct methods, use of Doppler, plethysmography and radioisotope studies (2). During surgery, backflow pressure, flow measurements and operative angiography have been used. O'Donnel used a simulated pulse wave not only to gauge distal flow, but also to assess postoperative patency (3).

Direct measurement of arterial outflow capacity at surgery might be helpful in determining the likelihood of success or failure of the procedure and in detecting distal obstructions not previously noted by angiography. It could also indicate the need for distal operative arteriography or more distal bypass.

Materials and Methods

For the past eighteen months we have been using simulated outflow capacity (S.O.C.) measurement during operative procedures. The necessary equipment is readily assembled and is inexpensive (Table I).

The 50 cc glass syringe connects to the three-way adapter. One arm of the adapter is attached to the manometer that is held above the level of the working surface. The other arm is then attached to an in-dwelling catheter that is made as short as is convenient. The catheter may be of any material, but must have an internal diameter that is large enough to allow a flow of 250 cc to 300 cc per minute of normal saline at 100 mm Hg when not in the distal artery. The syringe and catheter are filled with heparinized solution (10 units/cc) and the catheter is fixed within the outflow artery with a vascular tape (Fig. 1). Backflow pressure is measured by setting the adapter to pressure. While observing the manometer and recording the time, 50 cc of solution is injected into the artery maintaining the pressure between the systolic and diastolic brachial arterial pressure. In most cases this was about 100 mm Hg. It requires little practice to maintain the manometer needle at a fixed predetermined point. The time of injection of the 50 cc is recorded. The procedure may be repeated if necessary. The S.O.C. is calculated by the formula (cc/min = 60/time in sec × 50).

Using blood as the fluid medium with a 2.5 mm catheter alone and within the distal artery, we found that flow ranged between 75% and 80% of the flow of saline. As the diameter of the catheter increased, or the outflow capacity increased, the flow rates for blood tended to approach those of saline. For this reason we have found it more convenient to measure flow rates with saline and estimate about 75% of this for blood.

The S.O.C. has proven useful and instructive in instances where outflow capacity was in question. The following cases are illustrative:

Case 1: A 75-year-old male had a resection of a ruptured abdominal aneurysm involving the bifurcation of the aorta. The left common iliac artery did not backbleed, and a balloon catheter could not be passed beyond the region of the inguinal ligament. Distal perfusion of saline at 100 mm Hg showed a S.O.C. of 250 cc per minute at the iliac artery. Anastomosis resulted in good flow and a femoral pulse.

Case 2: An 85-year-old female suffered an acute occlusion of the popliteal artery and was admitted several days after the acute episode. Angiography showed a nonocclusive thrombus at the level of a narrow adductor canal and complete occlusion of the popliteal artery and its branches. Popliteal artery exploration was performed and thrombotic material removed from the anterior and posterior tibial arteries to the ankle with no backbleed. The proximal thrombus was removed producing a good forward flow. Distal perfusion indicated an S.O.C. of 240 cc/min of saline. The arteriotomy was closed and pulsatile flow remained until the time when a mid-leg amputation was required because of irreversible distal necrosis.

From the Department of Surgery, City Hospital Center at Elmhurst nd Mount Sinai School of Medicine of The City University of New York, N.Y.

Requests for reprints should be sent to Pinkus H. Szuchmacher, M.D., 86-35 Queens Blvd., Elmhurst, N.Y. 11373.

TABLE I

List of Required Materials

50cc. Glass Syringe
Three-way Adapter
Any Soft Plastic Catheter with at least 2½mm. internal diameter
10units/cc Heparinized Saline or the Patient's Own Blood
Aneroid Manometer (gas sterilized)
Rubber Connecting Tubing
Timer

Case 3: A 70-year-old diabetic male with rest pain had a right iliac artery occlusion as well as a superficial femoral obstruction with poor distal runoff. The profunda femoris was diffusely sclerotic with beading well past the third branch. The backflow profunda pressure was 40 mm Hg and the distal S.O.C. at 100 mm Hg saline was 200 ml/min. An 8 mm dacron ilioprofunda bypass without profundaplasty was successful.

Case 4: A 68-year-old diabetic male with gangrene of the toes and a previous lumbar sympathectomy had diffuse disease of the vessels below a fairly good popliteal artery and a fair-sized dorsalis pedis artery with good Doppler sounds. Distal perfusion of the dorsalis pedis artery was 40 ml/min at 100 mm Hg, but no suitable vein could be found for bypass. A popliteal to dorsalis pedis with a impra-graft (Expanded PTFE) failed.

Case 5: A 68-year-old male with severe claudication had an angiogram suggestive of an obliterated superficial femoral artery and what appeared to be excellent popliteal and leg vessel runoff. S.O.C. of the upper popliteal artery was only 100 ml/min at 100 mm Hg saline. Repeat angiogram at the table showed an unsuspected 80% crescent shaped occlusion of the mid-popliteal artery. The S.O.C. in the distal popliteal at 100 mm Hg was 150 ml/min and distal bypass was successful.

Case 6: A 75-year-old male diabetic with rest pain had a superficial femoral artery occlusion and a reconstituted popliteal artery leading to a single tibial vessel. S.O.C. in the distal popliteal artery was 230 cc saline at 100 mm Hg pressure. Femoral popliteal bypass was successful.

Case 7: An 83-year-old female with artrial fibrillation had an acute occlusion of the left femoral artery three days prior to admission. A common femoral embolus was removed. The S.O.C. was 89 cc per min in the superficial and 125 cc/min in the profunda femoral artery using saline at 100 mm Hg. Embolectomy was successful.

Case 8: A 67-year-old female was admitted with impending loss of both limbs and only a faintly palpable left femoral pulse. On angiogram, the external iliac vessels as well as the superficial femorals were almost completely occluded. S.O.C. in the profunda femoral vessels was 175 cc on the right and 135 cc on the left. A right common iliac to both profunda bypass was successful.

Case 9: A 66-year-old male with claudication and paresthesia of the right lower leg had angiographic evidence of occlusion of the external iliac and superficial femoral arteries. S.O.C. of the profunda at 100 mm Hg was 150 ml/min. Endarterectomy of the external iliac artery was successful.

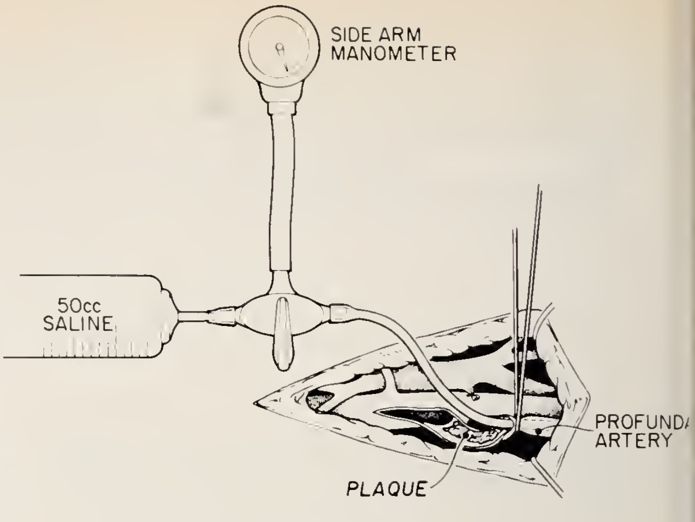

FIG. 1. Artist's drawing of procedure.

Case 10: A 70-year-old male had a right iliac artery occlusion with reconstitution of a small profunda and no common or superficial femoral artery. Profunda S.O.C. was 10 cc/min at 100 mg Hg saline. No vascular reconstruction was attempted because of the extremely low perfusion. A right lumbar sympathectomy was done.

Discussion

In the past, intraoperative evaluation of the potential success of arterial reconstitution or bypass has been based on intraoperative angiography, estimation of backflow and measurement of pressure. Simulated pulsed perfusion did not take into account pressure and volume flow (3). Simulated outflow capacity is not meant to be an absolute determinant of feasibility of successful reconstruction. The values obtained have varied from 10 mm/min to 300 ml/min. These values compare favorably with those obtained by various authors who used electromagnetic flow meters on the reconstructed vessels. (4–6). Occasionally, success has been obtained with extremely low flow rates and failures have occurred with high rates. In general, however, results of reconstruction are more favorable with higher flow rates. This method is meant as an additional guide for the surgeon when the success of a bypass is in doubt. At present we are continuing a prospective study to evaluate its efficacy and to evaluate which measurements below which reconstruction will probably fail.

Among the indications for S.O.C. measurement are: 1) Emergencies–ruptured aneurysm repair or embolectomies with poor backbleeding, 2) Bypass to isolated popliteal segments or to vessels with poor physical qualities, 3) Reassessment of runoff where the angiography may be misleading.

Summary

A method of estimating outflow capacity during vascular procedures that is safe, simple and easily performed, is described. The materials are inexpensive and are easily obtained and assembled. The values obtained compare favorably with those obtained by more sophisticated equipment and there is the added advantage of studying the vessels while they are still open.

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Purulent Cryptococcal Meningitis

STEPHEN J. KORNFELD. M.D., GARY P. WORMSER, M.D., DEBORAH BLUM, M.D., AND, CAROL SINGER, M.D.

Abstract

The cerebrospinal fluid formula in cryptococcal meningitis is classically described as showing a mild elevation in white cell count with a mononuclear predominance. Three patients with documented cryptococcal meningitis are described with spinal fluid examinations showing a high white cell count with a large polymorphonuclear predominance simulating a pyogenic meningitis.

The diagnosis of cryptococcal meningitis, at times, can be an elusive one. The usual clinical symptoms of headache, disturbance of consciousness, low grade fever, nausea, vomiting, and visual disturbances are nonspecific (1, 2). The cerebrospinal fluid examination in cryptococcal meningitis is classically described as showing a mild elevation in white count with a predominance of lymphocytes and a low glucose; but in fact, these findings can be quite variable and on occasion misleading to the physician (1, 3). Although it is well known that the cerebrospinal fluid glucose in cryptococcal meningitis may be normal in up to forty-five percent of cases, it is less widely appreciated that the spinal fluid may show not only an extremely elevated white count, at times in excess of fifteen hundred cells per cubic millimeter, but may also show a preponderance of polymorphonuclear leukocytes (1, 4, 5). In this report, three patients with documented cryptococcal meningitis are discussed whose spinal fluid examinations showed a high white cell count with a large predominance of polymorphonuclear leukocytes mimicking pyogenic meningitis.

The first patient was hospitalized at The Mount Sinai Hospital of New York, while the latter two patients were diagnosed at the Memorial Sloan-Kettering Cancer Center and are included in a recent review of cryptococcosis (6). Table I summarizes the pertinent clinical and cerebrospinal fluid findings of these patients. They did not differ significantly from other patients with cryptococcal meningitis in regard to their underlying diseases, clinical presentation and response to therapy.

Cases 1 and 2 had multiple spinal taps showing a high white cell count and a large predominance of polymorphonuclear leukocytes whereas Case 3 exhibited this picture only on the first spinal tap. Because of the exact simulation of a purulent meningitis, two of the three patients were initially treated for bacterial meningitis, and in one case this resulted in a seven-day delay before proper therapy was instituted.

In most cases of cryptococcal meningitis, the diagnosis can be made by demonstrating the yeast-like fungus on India ink preparation or by culture of the cerebrospinal fluid. However, even repeated India ink examinations may be negative in a large percentage of cases and growth in culture may be delayed or absent (1, 4, 7, 8). Serologic detection of cryptococcal antigen in cerebrospinal fluid may be the earliest and sole confirmation of the diagnosis in certain cases (4, 8). One of the most important aspects in the diagnosis of cryptococcal meningitis is that culture, India ink examination and serologic tests may all be negative with any single cerebrospinal fluid specimen and therefore diagnostic studies performed with multiple samples may be required.

It is important to appreciate the wide variation in cerebrospinal fluid findings that patients with meningeal cryptococcosis may exhibit. Without a high index of suspicion for cryptococcal meningitis, patients may be erroneously diagnosed as culture negative bacterial meningitis and, therefore, have appropriate therapy delayed. Hence, complete evaluation of a culture negative meningitis, even in the presence of an elevated cerebrospinal fluid white cell count with a predominance of polymorphonuclear leukocytes, should include repeated studies for cryptococcosis including India ink preparations, fungal cultures and assays for cryptococcal antigen.

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From the Departments of Medicine and Infectious Disease, Mount Sinai School of Medicine of The City University of New York, and the Memorial Sloan Kettering Cancer Center, New York, N.Y.

Requests for reprints should be sent to Gary Wormser, M.D., Chief, Infectious Disease Section, Veterans Administration Hospital, 130 West Kingsbridge Road, Bronx, N. Y. 10468.

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TABLE I

Clinical and Laboratory Summary of Three Patients with Purulent Cryptococcal Meningitis Lumbar Puncture Results Prior to Antifungal Therapy

Patient	Age	Sex	underlying disease	immunosuppressive therapy at time of diagnosis	initial antibiotic treatment	opening pressure	protein mg %	glucose mg %	RBC mm^3	WBC mm^3	% polys	% monos	culture	india ink	cryptococcal antigen
#1	62	F	chronic active hepatitis	immuran prednisone	chloramphenicol ampicillin	210	59	13	10	859	88	12	Cryptococcus neoformans	+	— by complement fixation
#2*	75	F	polycystic kidney disease with chronic renal failure	none	penicillin chloramphenicol streptomycin	200	65	† N.D.	0	79	90	10	Cryptococcus neoformans	N.D.	N.D.
						120	N.D.	N.D.	0	36	76	24	Cryptococcus neoformans	+	N.D.
#3	38	M	Hodgkins disease	prednisone vinblastine	none	285	178	32	0	204	95	5	Cryptococcus neoformans	–	N.D.

* Lumbar punctures were performed on day one and two of hospitalization respectively.

† N.D. = Not Done.

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Nonsurgical Treatment of Cerebellar Hematoma

WILLIAM H. THEODORE, M.D., JEFFREY STRIAR, M.D., AND ANDREW BURGER, M.D.

Abstract

Five patients, aged 61–70, were admitted with acute hypertensive cerebellar hemorrhage to The Mount Sinai Hospital Neurology Service over a three-year period. They were diagnosed by computerized tomography (CT Scan), and treated nonsurgically with steroids, antihypertensive medication, and supportive care. Clinical findings were suggestive of, but not diagnostic of, cerebellar hemorrhage. No patient was comatose, but three showed a definite disturbance of consciousness. Extensor plantar responses were present in all five cases. Fluctuating signs of posterior fossa dysfunction led to consideration of other diagnostic categories including ischemia and neoplastic disease. Computerized tomography demonstrated a high density hematoma of less than three centimeters in maximal diameter in each case, as well as compression of the fourth ventricle, and hydrocephalus was indicated in two patients. Sequential CT Scans demonstrated resolution of the hematomas. Recovery was uncomplicated and all patients were alive six months after discharge. Two showed mild to moderate residual disability, one of whom had a history of a previous cerebrovascular accident. One patient died one year after discharge from an acute myocardial infarction. Although they became ill precipitously, they appear to represent a more benign part of the spectrum of acute cerebellar hemorrhage, which may safely be managed medically.

Introduction

Though cerebellar hematomas are not infrequently encountered, their precise incidence is unknown. Large autopsy series suggest they constitute approximately ten percent of all intracranial hemorrhages (1, 2). Most authors recommend surgical intervention as the treatment of choice. In the past, many authors had recommended that emergency surgery should be performed without waiting for angiography to confirm the diagnosis (3–5).

The advent of computerized tomography has facilitated early diagnosis of cerebellar hematoma (6). Recently, Heiman and Satya-Murti reported two cases of recovery from acute cerebellar hematoma in which surgery was withheld due to systemic disease (7). Little et al reported four further cases of recovery with nonsurgical therapy (8). These patients were, it was felt, distinguished from those requiring surgery, in that they had no disturbance of consciousness on initial medical evaluation, and had no hydrocephalus on CT Scan.

In the past three years, five patients were seen on the Neurology Service of the Mount Sinai Hospital, each of whom recovered without surgery. These patients had more severe clinical involvement, as well as more extensive findings on CT Scan, than those reported by Little et al, and appeared to extend the spectrum of acute cerebellar hematoma that may be managed medically (8).

Case Reports

Case 1: A sixty-five-year-old hypertensive male was admitted to another hospital on October 10, 1975, following the sudden onset of severe headache, nausea and vomiting. Five days later the patient was transferred to The Mount Sinai Hospital. He was lethargic, but responsive to verbal stimuli. Blood pressure was 160/90 mm Hg. Cheyne-Stokes respirations were present. There was a left gaze preference, with limitation of conjugate gaze to the right, and nystagmus on right lateral gaze. There was no papilledema, and pupils were equal and reactive to light. There was mild peripheral right facial paresis, dysarthria, and right hemidystaxia. Bilateral Babinski signs were present. Routine laboratory studies were normal. Cerebrospinal fluid was clear and colorless without cells, the protein was 46 mg%. Electroencephalogram (EEG) showed diffuse cerebral dysfunction. Seventeen days after the onset of the illness the patient had a CT Scan that revealed a three centimeter hematoma in the right cerebellar hemisphere. Bibrachial angiography showed a right cerebellar avascular mass. The patient was placed on 4 mg of decadron intravenously (IV) every

From the Department of Neurology, The Mount Sinai Hospital and Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to Dr. Andrew Burger, Department of Neurology, The Mount Sinai Hospital, New York, N.Y. 10029.

six hours. A repeat CT Scan on November 18, 1975, showed a reduction in the size and density of the hematoma. The patient was discharged on November 30, 1975, with mild residual dystaxia. By June, 1976, he had returned to work. CT Scan on August 5, 1976, showed complete resolution of the hematoma.

Case 2: A sixty-one-year-old hypertensive female was admitted to The Mount Sinai Hospital on December 24, 1976, with acute onset of vertigo, nausea, vomiting and gait disturbance. She was disoriented, but responsive to verbal stimuli. Blood pressure was 230/160 mm Hg. There was no papilledema. Pupils were equal and reactive. The patient had skew deviation with ocular dysmetria and nystagmus on right lateral gaze. Paresis of upward gaze and conjugate gaze to the right were noted. There was no facial weakness. Speech was dysarthric. Examination showed right arm pronator drift, bilateral Babinski signs, right hyperreflexia, dystaxia on finger-to-nose and heel-to-shin testing (left greater than right), and marked trunkal dystaxia. Cerebrospinal fluid was grossly bloody. The supernatant was xanthochromic. Opening pressure was 200 mm water. The patient was started on 4 mg decadron IV every six hours with marked improvement in mental status in two days. CT Scan on December 27, 1976, showed a left cerebellar hematoma. The fourth ventricle was compressed and not well visualized, and there was evidence of obstructive hydrocephalus. Bibrachial angiography showed an avascular mass in the midline posterior fossa. EEG showed diffuse cerebral dysfunction. Repeat CT Scan on January 5, 1977, showed reduction in the size and density of the hematoma. Hydrocephalus was still present. Steroids were continued through February 6, 1977, when the patient was able to walk with assistance, but tended to fall to either side with persistent mild dystaxia. CT Scan on January 30, 1977, showed no significant change in ventricular size, but there was further resolution of the hematoma itself. One year after discharge the patient had a normal neurological examination, but then died suddenly of an acute myocardial infarction.

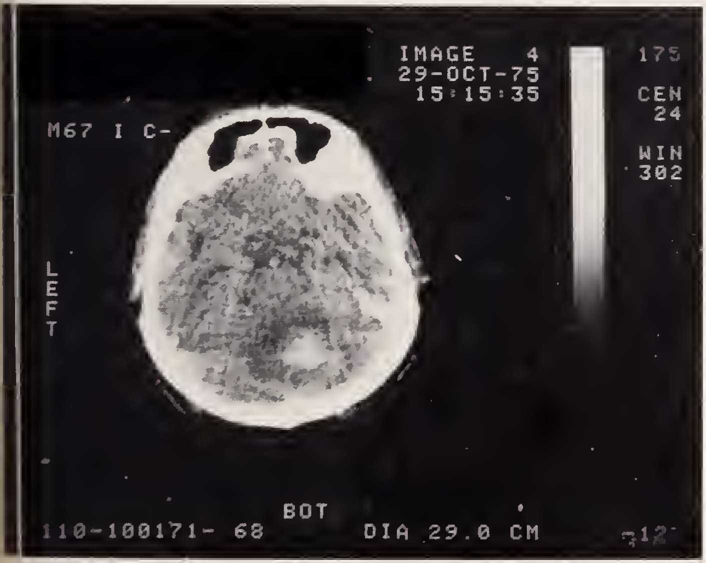

Fig. 1. Patient one. CT Scan dated October 29, 1975, done without contrast material shows a large hematoma in the right cerebellar hemisphere. There is collapse of the fourth ventricle.

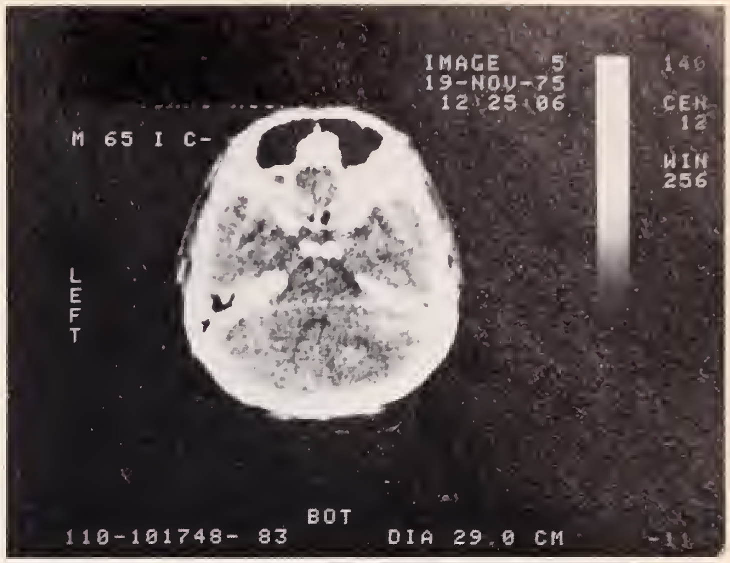

Fig. 2. Patient one. Follow-up scan dated November 19, 1975, done without contrast shows partial resolution of the hematoma. The fourth ventricle is now visualized.

Case 3: A sixty-six-year-old hypertensive female taking ten mg of prednisone daily for rheumatoid arthritis was admitted to The Mount Sinai Hospital on April 1, 1977, with a six-day history of headache, dizziness, and ataxia. There was no nausea or vomiting. Blood pressure was 170/100. She was alert and oriented with impaired calculations and mild recent memory deficit. Fresh flame-shaped hemorrhages were noted in both fundi, the disc margins were distinct. Horizontal nystagmus was noted on lateral gaze bilaterally. The gait was broad-based with trunkal dystaxia. Dystaxia was noted on heel-to-shin testing but absent on finger-to-nose testing. Bilateral Babinski signs were present. Prednisone was increased to 40 mgm, per day. A CT Scan on April 5, 1977, showed a left cerebellar hematoma. Cerebrospinal fluid was clear and colorless with an opening pressure of 170 mm water. Protein was 64 mgm%. CT Scan on April 21, 1977, demonstrated resolution of the hematoma. Steroids were tapered to the original dose of 10 mgm daily. The patient was completely well on follow-up examination through August, 1978.

Case 4: A sixty-two-year-old hypertensive female developed severe headache, ataxia, and pain over the right side of the face in a period of two hours. On admission to another hospital on October 7, 1977, she was noted to have a blood pressure of 260/150 mm Hg. The patient

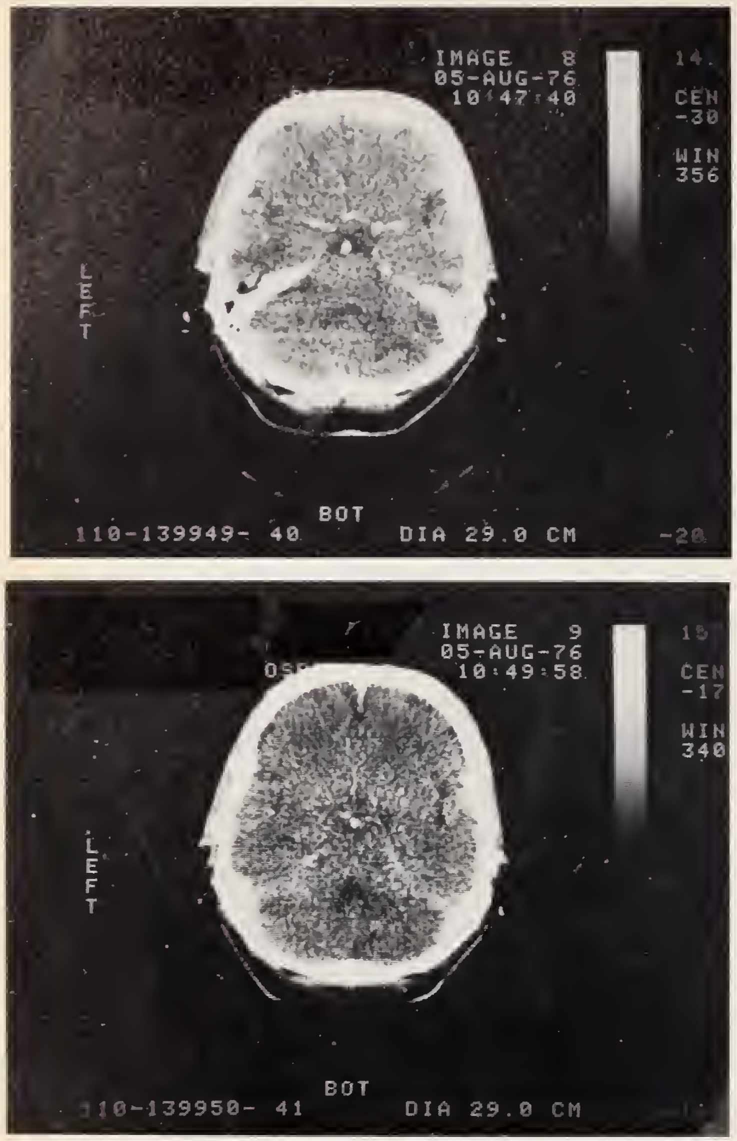

FIG. 3, 4. Patient one. Follow-up scan dated August 5, 1976, done with contrast material. There is now an area of decreased density in the right cerebellar hemisphere and the fourth ventricle is enlarged. There is no evidence of a space-occupying lesion.

was lethargic, but oriented. There was no papilledema, pupils were equal and reactive to light. Nystagmus was present in all directions of gaze. There were bilateral sixth nerve paresis, right peripheral facial paresis, dysarthria, right limb and trunkal dystaxia. Bilateral babinski signs were present. Routine laboratory studies were normal. Cerebrospinal fluid was clear and colorless. The protein was 33 mgm%. EEG showed diffuse cerebral dysfunction. CT Scan revealed a right cerebellar hematoma, with compression of the fourth ventricle and hydrocephalus. The patient was given 16 mgm decadron IV daily and transferred to The Mount Sinai Hospital. Bibrachial angiography showed a right cerebellar avascular mass. The patient made a rapid improvement, steroids were tapered, and she was discharged on November 20, 1977. CT Scan before discharge showed a persistent hematoma. She has remained well on follow-up examination.

Case 5: A seventy-year-old hypertensive male with a history of myocardial infarction in 1974, developed left central facial weakness one month prior to admission. Two weeks before admission he had an episode of vertigo lasting several minutes. He fell but did not lose consciousness. On the day of admission, July 29, 1978, he developed vertigo, nausea, and inability to keep his balance. Blood pressure was 200/140 mm Hg. Pulse was 64 and regular, with episodes of sinus bradycardia at 45–55. Fundi were normal. Pupils were equal and reactive. There was nystagmus on right lateral gaze, and rotatory nystagmus on upward gaze. A left central facial paresis, dysarthria, and right hemiataxia were present. There was a right extensor plantar response. The creatine phosphokinase was 1657 mu, and the MB band was trace positive. Lactic dehydrogenase was 330. Electrocardiogram (ECG) showed left ventricular hypertrophy and bundle branch block, unchanged from previous records. Initially the patient became more lethargic, and developed a right hemiparesis. A CT Scan showed a right cerebellar hematoma. Surgery was considered, but the patient responded swiftly to 4 mgm IV decadron every six hours, and operation was withheld although subsequent ECG's showed no evidence of acute myocardial infarction. He continued to improve, steroids were tapered, and he was discharged to go home on September 16, 1978, with residual right hemiataxia, able to walk with assistance. CT Scan before discharge showed almost complete resolution of the hematoma.

Discussion

The presentation in each of our cases was consistent with cerebellar hematoma, but other diagnoses could not be excluded clinically. Some authors have emphasized particular combinations of signs and symptoms as pathognomonic. Ott et al found 73% of their patients had at least two signs out of the triad of appendicular ataxia, ipsilateral gaze palsy, and peripheral facial palsy (5). Fisher et al emphasized small, reactive pupils, impaired conjugate gaze, nystagmus, facial weakness, diminished ipsilateral corneal response, and ataxia (4). They stated that dysarthria was "an almost constant clinical sign," but concluded that "the clinical picture is polymorphic." Other writers have stressed the difficulty of clinical diagnosis (1, 9–11). Rosenberg and Kaufman found the correct diagnosis was made in only thirteen of thirty-three patients suspected to have, or eventually proved to have, a cerebellar hematoma (12). The presentation overlaps with that due to cerebellar or pontine infarction (2, 13–15). Since many of the symptoms are caused by brainstem compression, fluctuating findings may confuse the clinical picture (4).

In our series, computerized tomography confirmed the diagnosis. Angiography excluded less common etiologies, such as arteriovenous malformation, and showed an avascular mass in the cases in which it was performed.

Results of therapy have been difficult to evaluate. In the series of Ott et al, the state of consciousness on admission and rate of progression of symptoms seemed to be the most important prognostic factors (5). Surgical and nonsurgical groups have not been strictly comparable. Comatose patients have more often been treated nonsurgically. In the recent series of Brennan and Bergland, all three nonoperated patients that died were comatose on admission. Two had ataxic respirations and two had absent caloric responses. Of the nine surgically treated patients, three were comatose on admission and also died.

In our series, all patients were awake on admission and responsive to verbal stimuli–although three showed a definitely impaired state of consciousness. They had all become ill "acutely," but had survived several days to weeks before the diagnosis was confirmed. Since the patients were clinically stable it was elected to treat them with steroids.

Sequential CT scanning was valuable in following the resolution of the lesions. The distortion of the fourth ventricle and hydrocephalus that was seen initially in two cases was resolved on subsequent scans.

Previous reports have pointed to a group of patients similar to ours, conscious but lethargic on admission, often with a delay in diagnosis or slow evolution of symptoms, who recovered without surgery (4, 11). Ott et al noted that after eight days there was no statistical advantage in anticipating clinical deterioration by operating on stable patients (5). They felt, nevertheless, that patients stable for up to eight weeks ought to have their hematomas evacuated. It is likely that, with the increased use of CT scanning, patients overlooked in the past will be discovered to have cerebellar hematomas. One may expect that the type of patient reported here will be seen more frequently, and the spectrum of disease may be broader. It is important to try to establish criteria for selecting a patient who may be safely managed medically.

Our patients differed from those of Little et al in that three showed a definite disturbance of consciousness (8). All had either unilateral or bilateral Babinski signs, as well as more severe dystaxia and cranial nerve involvement. Although only one of our patients had a hematoma that measured as much as three centimeters, two showed significant hydrocephalus on CT Scan.

Freeman et al recently reported a nonoperated patient who survived cerebellar hemorrhage with significant neurologic residual (16). They felt that the benign course of Ott's medically treated patients was "surprising." In Ott's series, two-thirds of each group of twelve surgically and nine medically treated patients were well on long-term follow-up study (5). Four of our five patients were able to return to a normal life. Of the two patients with persistent neurologic findings, one had had a previous cerebrovascular accident. The data available from these and other studies do not support the conclusion that surviving patients treated surgically have less residual disability.

A controlled study of cerebellar hemorrhage has not been performed.

Our experience shows, however, that patients who survive the initial ictus, and do not have a marked alteration of consciouness, may be followed without surgery if their clinical picture is stable. Steroids and osmotic agents should be used. The presence of long tract, oculomotor, or cranial nerve dysfunction in our cases did not indicate a poor prognosis. Sequential CT Scans are necessary to document resolution of the hematoma and reduction of the mass effects. Patients should be hospitalized long enough for marked improvement of neurologic findings. Steroids should be tapered before discharge to be sure that signs and symptoms of a residual posterior fossa mass lesion are not being masked.

We believe that once the diagnosis of cerebellar hematoma is established by CT Scan, management should be tailored to the needs of the individual patient. Relative contra-indications to surgery, such as clotting disorders, metastatic carcinoma, or the systemic complications of hypertension and vascular disease, may be taken into account. Surgery should be reserved for those patients with a fulminating presentation or deteriorating course.

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Pulmonary Edema Occurring During Emergence from Anesthesia

MARGARET G. PRATILA, M.D. AND VASILIOS PRATILAS, M.D.

A case of pulmonary edema, following anesthesia for termination of pregnancy, is presented as arising in a young healthy patient, age 17. Reflex sympathetic stimulation and the antidiuretic action of oxytocin are discussed as possible contributory factors.

Case Report

The patient, 17 years old, weighing 68 kgs, was admitted on an ambulatory basis on the day of surgery for elective termination of pregnancy. There was no significant history of medical or allergic problems. She denied taking medications and the laboratory findings were normal. For premedication, she received atropine sulphate 0.4 mgs intravenously, prior to induction of anesthesia achieved by the administration of thiopental 250 mgs. Anesthesia was maintained by the administration of a 5/2.5 nitrous oxide/oxygen mixture. The total gas flow being 7.5 liters per minute. The airway was secured with a medium-sized plastic airway. Relaxation and control of respiration was obtained following the administration of a 0.1% infusion of succinylcholine. After the surgery had been completed uneventfully, the nitrous oxide was discontinued. It was then noticed that the blood pressure (140/80 mm/Hg throughout surgery) had risen to 200/100 mm Hg. This rise was accompanied by profuse sweating, inadequate respiration and failure to regain consciousness. Rales could be heard over the entire lung field.

Diagnosis of pulmonary edema was made and the patient was treated with furosemide (20 mg intravenously) and the institution of positive pressure ventilation after the trachea had been intubated with a 7.5 mm (I.D.) oral tracheal tube. Following intubation, large quantities of frothy white sputum were aspirated. A central venous line was secured and measurement of the central venous pressure revealed it to be 12 cm H_2O.

In response to the furosemide, diuresis occurred and the pulmonary edema subsided rapidly. The central venous pressure fell to 7 cm H_2O and the blood pressure dropped to 120/80 mm of Hg. The inadequate respiratory pattern returned to normal. This coincided with the return to consciousness and the endotracheal tube was removed without incident.

A chest x-ray taken 1½ hours after the episode of pulmonary edema was normal. The patient's postoperative course was uneventful and discharge was possible two days later.

Discussion

Adriani described six causes of pulmonary edema associated with anesthesia and surgery (1):

Incomplete cardiac emptying due to myocardial depression, tachycardia or dysrhythmia

Both nitrous oxide and sodium thiopental are capable of producing myocardial depression. However, anesthetic agents are rarely the sole cause of pulmonary edema, especially in a young, healthy adult. In this patient, the time sequence would preclude myocardial depression as being the cause. Neither tachycardia nor dysrhythmia occurred. These can be excluded as precipitating factors.

Shift of fluid to the pulmonary vascular bed

The peripheral vascular bed is very sensitive to vasoconstrictor influences. Peripheral vasoconstriction may cause a shift of blood into the pulmonary vascular bed. This is less vasoactive and pulmonary edema may occur.

Pulmonary edema has been produced by sustained administration of epinephrine. The main factor in epinephrine-induced pulmonary edema appears to be the enormously increased hydrostatic pressure in the pulmonary vascular bed (2). Neurogenic pulmonary edema is thought to follow maximal central sympathetic discharge (3). This would produce an intense but transient generalized vasoconstriction. Blood would then shift from

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From the Department of Anesthesiology, Beth Israel Medical Center and Mount Sinai School of Medicine (CUNY). New York, N.Y.

Requests for reprints should be sent to M. G. Pratila, M.D., 150 East 69th Street, New York, N.Y. 10021

the high-resistance systemic circulation to the low-resistance pulmonary circulation. Pronounced increases in pulmonary vascular pressure and blood volume then would produce pulmonary edema–a consequence of the hydrostatic effect of the increased pulmonary capillary pressure.

It is possible that afferent impulses reaching the hypothalamus during withdrawal of anesthesia may cause sufficient disturbance of hypothalamic function to produce the massive alpha-adrenergic discharge.

Theodore and Robin noted that pulmonary hypertension and hypervolemia injure pulmonary blood vessels, altering pulmonary capillary permeability and resulting in lung hemorrhage (3). Thus, after transient, systemic and pulmonary vascular hypertension subsides, abnormal pulmonary capillary permeability persists and pulmonary edema may be present in the presence of normal hemodynamics and cardiac function. This factor, possibly, contributed to the onset of pulmonary edema in this patient. Rapid emergence from light anesthesia, in the presence of pain from surgical intervention and uterine contractions, may have initiated this reflex.

Negative airway pressure

Respiration was controlled or assisted throughout the procedure. There was no respiratory embarrassment until the onset of the edema.

Circulatory overload

The patient received 500 ml of 5% dextrose in Ringer's lactate. She had no oral fluids since 10 p.m. the previous evening (a total of 16 hours). An absolute overload of fluid is obviously unlikely. However, 20 units of oxytocin were added to the infusion of which she received 7.5 units.

Lauersen and Birnbaum have described four cases of water intoxication associated with oxytocin administration during saline-induced abortion (4). It has been shown that administration of oxytocin may have an antidiuretic effect in clinical practice. Oxytocin has a direct action on the kidney (5). This action may preceed its oxytocic effect and begin an infusion rate of 15 mU/minute and is maximum at 45 mU/m. The patient received 7.5 units over a period of 10-15 minutes and certainly achieved this dosage.

While in the majority of reported cases, water intoxication with its production of muscular irritability and convulsions is indicated as the clinically observed effect of oxytocin, we believe it, along with the shift of fluid to the pulmonary vascular bed, contributed to produce pulmonary edema in the patient.

Idiopathic

Direct injury of the alveolar membrane

The purity of modern agents negates a chemical cause for the pulmonary edema. However, aspiration of gastric content remains a possibility. This cannot be dismissed, particularly in an ambulant patient. The rapidity with which the chest cleared, in the absence of aggressive therapy, would tend to suggest that aspiration was not the cause.

Summary

The case of a 17-year-old patient who developed pulmonary edema at the termination of anesthesia for interruption of pregnancy was described. Multiple factors were discussed. It is the opinion of the authors that the edema was the result of reflex adrenergic discharge in combination with the administration of oxytocin. The patient's condition was readily treated by the administration of furosemide and the institution of positive pressure ventilation with an augmented inspired oxygen concentration.

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Neurologic-Neurosurgical Notes

ALLAN E. RUBENSTEIN, M.D. AND MARTIN H. SAVITZ, M.D., COEDITORS

Hemicraniectomy, Hydrocephalus, and Hemispheric Dysfunction Following Shunting: Case Report

MARTIN H. SAVITZ, M.D., ERNEST S. MATHEWS, M.D., AND HIROSHI NAKAGAWA, M.D.

In the treatment of acute subdural hematoma, hemicraniectomy was devised to adequately decompress the edematous brain, totally remove holoconvexity clots, and extensively visualize the cerebral cortex for hemostasis (1). Although the initial survival statistics were quite encouraging, subsequent experience with the procedure was not gratifying (2). Progressive focal neurological deficit after a successful hemicraniectomy has been attributed to the gradient between atmospheric and intracranial pressure (3). The same mechanism has been proposed for transient hemispheric dysfunction in the presence of a postoperative skull defect and cerebrospinal fluid leak following intraoperative drainage from the lumbar theca (4). The purpose of this paper is to report the neurological complications of a large cranial defect, the alterations after a ventriculoperitoneal shunt for posttraumatic hydrocephalus, and the improvements following cranioplasty.

Case Report

A 19-year-old girl fell from a moving vehicle and struck her head directly on the pavement. After admission to the emergency room, there was an episode of vomiting followed by a grand mal seizure with her eyes deviated to the right side. Significant findings in the physical examination were swelling of the left temporoparietal scalp and gross blood in the right external auditory canal.

She was noted to be stuporous, but responded to painful stimuli by flexion movements of all limbs. The pupils were small, equal, and minimally reactive to light. Deep tendon reflexes were brisk, and no pathological reflexes were elicited.

Skull x-rays revealed a left parietal linear fracture. 10 mg of dexamethasone and 100 gm of mannitol were given intravenously, and phenobarbital, 60 mg, intramuscularly. Bilateral carotid angiograms demonstrated diffuse areas of swelling on both sides of the brain as well as an extracerebral collection over the left convexity, spasm of the left middle cerebral artery, and a 5 mm midline shift of the anterior cerebral arteries from left to right.

The patient was taken to the operating room and underwent left hemicraniectomy. About 5 cc of epidural hematoma and a subdural collection of blood over 50 cc were evacuated. There were multiple areas of pial discoloration consistent with cerebral contusion. The frontotemporoparietal bone flap was not replaced in order to provide maximal mechanical decompression of the swollen brain.

Postoperatively, wound healing was unremarkable; she was able to converse with fair orientation. On the tenth hospital day, dysphasia and right hemiparesis developed. Repeat cerebral arteriography showed herniation of the brain through the skull defect, ventricular dilatation, and continuing spasm of the left middle cerebral artery. By the third hospital week, the patient could speak in short phrases and ambulate with assistance; there was marked weakness of the intrinsic muscles of the right hand. Pulsations of the brain were observed; she was fitted with a protective helmet and discharged home in the care of her family.

Ten days later, lethargy and confusion were noted. On readmission to the hospital, she manifested right facial asymmetry, right hemiparesis, right hyperreflexia, and a right Babinski sign. The hemicraniectomy site was tense.

From the Department of Neurosurgery, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to: Martin H. Savitz, M.D., Department of Neurosurgery, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, N. Y. 10029.

Computerized axial tomography revealed porencephalic cyst formation, diffuse ventricular dilatation, herniation of the brain through the skull defect, and a midline shift (Fig. 1). Lumbar puncture demonstrated an opening pressure of 200 mm of water. An intrathecal scan, performed with In^{180}, was consistent with communicating hydrocephalus.

Ventriculoperitoneal shunting allowed the brain to recede within the cranial vault, and pulsations were again seen. Repeat computerized axial tomography showed the position of the ventricular catheter and early disappearance of the irregular lucency in the left temporal lobe (Fig. 2). Initially, her mental status and motor power were greatly improved; but whenever she was brought upright, the hemicraniectomy site became scaphoid, and the left hemispheric dysfunction was exacerbated. Accordingly, she was nursed in a reclining position and allowed out of bed for only short periods of time.

One month later, a cranioplasty was performed with steel screen and methyl-methacrylate. The cosmetic result was good and the patient was mobilized. Intensive physiotherapy and speech therapy continued over a one-year period. A follow up scan documented resolution of the ventricular dilatation and porencephalic cyst formation (Fig. 3). Three years after her head injury, she has completed two semesters of college; the only finding on her neurological examination is minimal weakness of the intrinsic muscles of the right hand.

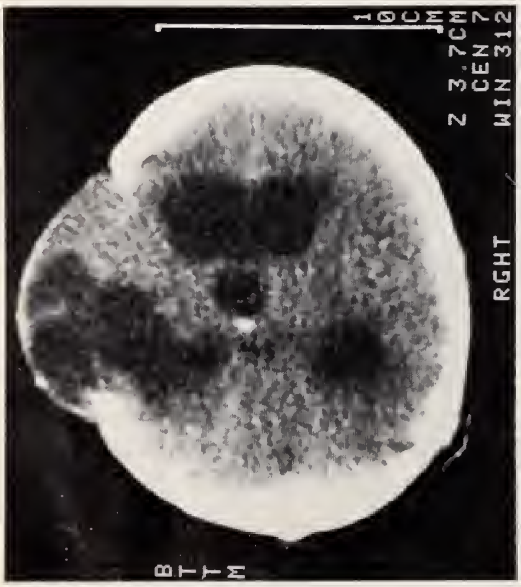

FIG. 1. Note irregular lucency in left temporal lobe, ventricular enlargement, herniation of brain substance, and right to left shift of pineal gland.

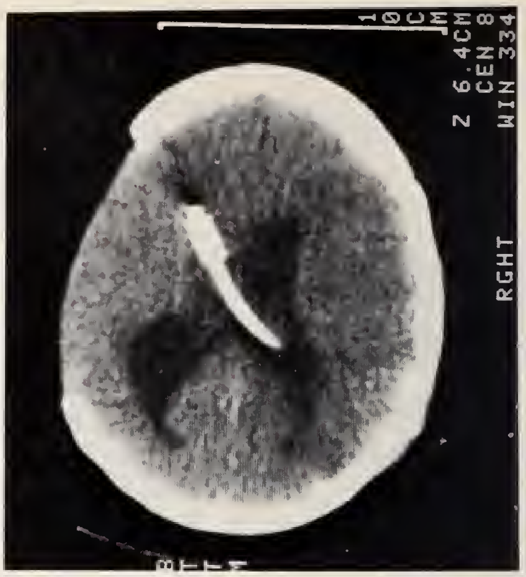

FIG. 2. Note placement of ventricular catheter in left frontal horn through septum pellucidum and resolution of porencephalic cyst formation.

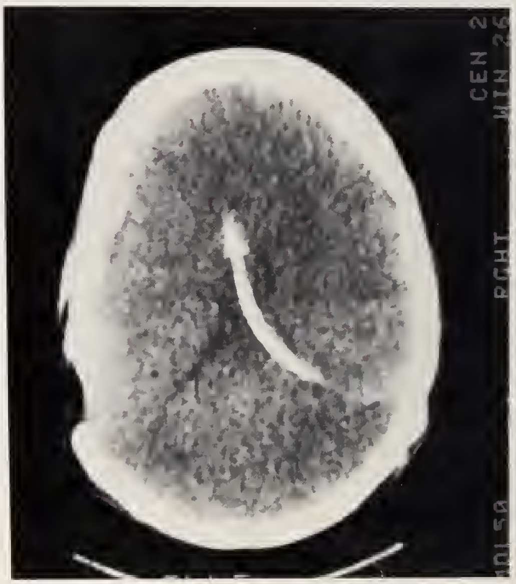

FIG. 3. Note slit-like ventricles and midline pineal gland.

Discussion

Functional recovery after acute subdural hematoma has been almost universally disheartening, even though reported survival rates have differed with various neurosurgical procedures (1, 2, 5–8). The vast majority of hemicraniectomies were performed on males, craniocerebral trauma due to falls rather than moving vehicular accidents, patients over 40 years of age, and cases with neurological signs of brainstem injury (2). Our own case of functional recovery shared little in common with these statistics gathered from the world literature.

Ventricular dilatation following head injury and subarachnoid hemorrhage is well known and, in its common form, self-limiting (9). Communicating hydrocephalus results from obstruction of the arachnoid villi or interruption of flow of cerebrospinal fluid through the basal cisterns by the accumulation of blood. Less than half of the cases confirmed by intrathecal scanning with radioiodinated serum albumin are associated with increased intracranial pressure. The cerebrospinal fluid pressure in our own case was elevated even in the presence of a decompressive craniectomy.

Tabaddor and LaMorgese (3) reported a case of progressive cortical damage caused by direct pressure of the scalp through a large cranial defect remaining after evacuation of an acute subdural hematoma; complete neurological recovery was observed following cranioplasty. Guido and Patterson described the combination of a postoperative skull defect and a persistent cerebrospinal fluid leak through lumbar puncture sites causing a transient focal neurological deficit in two patients; prompt resolution resulted when the holes in the meninges for intraoperative drainage were sealed with epidural blood patches (4). Transmission of external pressure to the intracranial fossa could not occur in our own case until ventriculoperitoneal shunting allowed lowering of the cerebrospinal fluid pressure below atmospheric pressure whenever the patient was erect. Residual damage to the vasculature of the brain from prolonged spasm also contributed to compromise of the regional cerebral blood flow.

Summary

A report of acute subdural hematoma in a 19-year-old girl with good functional recovery is presented. The case was initially treated successfully by hemicraniectomy, but subsequently complicated by cerebral vasospasm, porencephalic cyst formation, and posttraumatic hydrocephalus. Ventriculoperitoneal shunting was followed by intermittent left hemispheric dysfunction which resolved after cranioplasty. The mechanisms causing high and low cerebrospinal fluid pressure syndromes are discussed.

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The Students' Corner

Paul Celano, B.A., Editor

Nephelometric Determination of Immunoglobulins in Exocrine Pancreatic Secretion: Studies on Patients with and without Pancreatic Disease

NEIL J. FINKLER, B.A.*, MELISSA PALMER, B.S.*, MARGOT GONDA, M.S. and DAVID A. DREILING, M.D.

Introduction

The secretory immune system is known to play an important role in maintaining normal physiology. Secretory immune deficiency in the respiratory tract, for example, often results in repeated infection and increased susceptibility to disease (1).

Estimation of immunologic activity has become an increasingly important factor in the diagnosis of diseased states. Recently, concentrations of IgG, IgM, and IgA in duodenal aspirates using a radial immunodiffusion technique have been shown to be of value in diagnosing pancreatic disease (2). Using the same procedure, Brasher et al reported detectable levels of immunoglobulins G, M, A, E, and D in pure human pancreatic fluid from two patients with pancreatic fistulae (3). The purpose of this study is to investigate the immunologic activity in exocrine pancreatic secretions in patients with and without pancreatic secretory dysfunction using a rate nephelometry technique.

Materials and Methods

This study was conducted on 49 patients that underwent pancreatic secretin tests at The Mount Sinai Hospital Pancreatic Research Laboratory. Of these 49 patients (24 males, 25 females), 25 had normal pancreatic function, 14 were diagnosed as having chronic pancreatitis, two had acute pancreatitis, four had cholecystitis, three had carcinoma, and one had a pancreatic pseudocyst.

The secretin test was performed on patients in the fasting state and was used for the estimation of pancreatic function and the diagnosis of pancreatic disease. Under fluoroscopic examination the double channel portion of the tube was positioned in the stomach, the single channel portion remaining in the duodenum with the tip of the tube reaching the Ligament of Treitz. After complete evacuation of the stomach and duodenal contents, 1.0 clinical unit of secretin per kilogram body weight was administered intravenously. Gastric and duodenal aspirates were obtained through a radioopaque tube kept under suction of 90 mm Hg using a Gomco pump. A basal twenty minute collection period was followed by further collection of gastric and duodenal specimens at specified time intervals. The duodenal juice was examined for bicarbonate concentration, volume (cc/kg), pH, amylase concentration, bile, and blood.

From these 49 patients, a total of 441 immunoglobulin determinations were made. Immunoglobulin G, M, and A were quantitated by rate nephelometry using the Beckman Immunochemistry Analyzer. This technique involved the measurement of the rate of increase in intensity of light scattered by particles suspended in solution as a result of larger complexes formed during the antigen-antibody reaction.

All specimens were stored at −20°C prior to immunoglobulin determination and all results were recorded in units of milligrams/deciliter.

From the Department of Surgery, Mount Sinai School of Medicine, CUNY, New York, N.Y. 10029.

Requests for reprints should be sent to Mr. Neil Finkler, Department of Surgery, Mount Sinai School of Medicine, One Gustave L. Levy Place, Annenberg 25-86, New York, N.Y. 10029.

* Volunteer Fellow, Department of Surgery

TABLE I

Diagnosis	N	IgG			IgM			IgA		
		Serum	Do	D	Serum	Do	D	Serum	Do	D
Normal	25	1716 ± 933	.19	.19	184 ± 115	.19	.19	296 ± 189	.19	.19
Chronic Pancreatitis	14	2213 ± 876	1.55 ± 2	.9 ± 1.2	247 ± 219	1.0 ± 1.9	3.7 ± 5.9	343 ± 150	3.8 ± 2.4	4.3 ± 3.3
Acute Pancreatitis	2	1940 ± 110	.8 ± .6	.19	110 ± 30	2.2 ± 2.0	.19	199 ± 74	1.6 ± .4	3.0 ± 2.1
Carcinoma	3	1570 ± 60	2.1 ± 1.7	.19	259 ± 64	6.3 ± 3.2	3.1 ± 3.3	273 ± 99	3.3 ± 1.8	7.2 ± 2.1
Pancreatic Pseudocyst	1	1060	.2	.7	134	2.3	1.6	453	7.6	13.5
Cholecystitis	4	1923 ± 543	.8 ± 1.1	2.1 ± 1.4	289 ± 190	5.9 ± 3.6	2.8 ± 2.6	325 ± 146	5.4 ± 3.4	2.8 ± 1.6

Mean Immunoglobulin (IgG, IgM, IgA) concentrations ± standard deviation in unstimulated (Do) and secretin stimulated (D) pancreatic secretion in patients with and without pancreatic disease.

Results

Immunoglobulin titers in serum, basal duodenal (Do) and post secretin duodenal (D) samples are shown in Table I. Values are expressed as mean concentration (mg/dl) ± standard deviation.

The lower limit of detecting immunoglobulin concentrations using the Beckman Immunochemistry Analyzer is .19 mg/dl. Samples in which the IgA titers were too low to register a reading were reported as <.19 mg/dl.

In order to test reproducibility of the Beckman Immunochemistry Analyzer, eight samples were run five times each. Results showed greater than 95% within-run precision for each sample tested.

Discussion

Quantitation of immunoglobulins has conventionally involved the method of radial immunodiffusion, a technique requiring time and technical precision. The kinetic approach to the measurement of antigen-antibody reactions offers the advantages of speed and ease of analysis coupled with the lack of need for blank measurements.

In all patients with normal pancreatic function (Do) and (D) IgG, IgM, and IgA concentrations were less than .19 mg/dl. Immunoglobulin determinations on basal duodenal and postsecretin duodenal samples from patients with pancreatic disease and cholecystitis revealed detectable levels of IgG, IgA and IgM in many cases. Of particular interest is IgA, the main component of secretory immunoglobulin. Detectable levels of basal duodenal and duodenal IgA were found in all patients with pancreatic disease and cholecystitis.

Duodenal IgA concentrations appear to parallel the extent of pancreatic involvement in the diseased state. The least severe pancreatic disorder dealt with in this study was mild acute pancreatitis with average IgA levels of 3.0 mg/dl. Patients with chronic pancreatitis, on the other hand, had higher average IgA levels such as 4.2 mg/dl. The IgA concentration was elevated in carcinoma of the pancreas to 7.2 mg/dl. Immunoglobulin A reached its highest value (13.5 mg/dl) in the duodenal sample from a patient with a pancreatic pseudocyst.

Although Tomasi et al were unable to detect pancreatic IgA using immunofluorescent labels, the increases in duodenal IgA following secretin injection indicate that the pancreas has immunoglobulin-producing capability in the diseased state (5). It is also possible that duodenal inflammation secondary to pancreatic disease results in additional immunoglobulin production from plasma cells lining the gut lamina propria.

The differences in duodenal IgA concentrations from one diseased state to another may provide the clinician with an additional criteria for assessing pancreatic function. Studies on a greater number of patients with pancreatic disease are necessary to further delineate the parameter patterns.

Summary

A simple nephelometric technique with high reproducibility has been utilized for determining immunoglobulin concentrations in pancreatic secretion.

The data from 441 determinations performed on 49 patients with and without pancreatic disease suggest that this parameter might be useful in the diagnosis of pancreatic disorders.

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Current Trends in Mammography

LAWRENCE GRUNFELD, B.S.

Introduction

Mammography has been used in the diagnosis of breast cancer since Salomon's work in 1913. It was not until the early 1960's that Gershon-Cohen and Egan, working independently, refined this technique to a form that was clinically acceptable (1). Recently, however, the trend has been toward caution in performing this procedure. Editorials such as John Bailar's "Mammography—A Time for Caution" and Swart's "The Risk of Mammograms" have appeared in JAMA (2, 3). In this paper I will review some of the literature dealing with the current application of mammography.

Discussion

One of the first reports that was critical of mammography was published by John Bailar of the National Cancer Institute (4). His criticism is based upon the Health Insurance Plan (HIP) study in New York City in which 62,000 women, aged 40–64, were followed in an effort to investigate the effectiveness of history, physical examination, and mammography in the detection of breast cancer. Bailar points out that of the 132 cases of carcinoma picked up in the screening, only 44 (15%) were detected by mammography alone, and not by physical examination. Assuming a 20%, seven-year mortality for those women with intraductal carcinoma and a 40%, seven-year mortality for the others, Bailar calculated that 14 deaths were to be expected in this group of 44 women. Actually, there were only two deaths, or a reduction of the mortality by twelve due to mammography.

The twelve-person reduction in mortality in the HIP study must be weighed aginst the risks of mammography. Based upon the National Academy of Science's Biological Effects of Ionizing Radiation (BEIR) report, there are six cases of breast cancer expected/1,000,000 women/rad of radiation/year following a ten-year latency period (5). In the HIP study, each woman received an average dose of two rads per mammogram. In other words, the 20,000 women receiving 6.4 rads/year for ten years would include eight cases of breast cancer produced by the screening.

Bailar further broke down his analysis by age groups (6). The calculated number of deaths caused by mammography was found to be greater than the number of lives saved by this procedure in women younger than 55 years of age. It is only for women older than 55 years of age that the benefit of mammographic screening outweighs the risks. Bailar concluded that, "the routine use of mammography in screening asymptomatic women may eventually take almost as many lives as it saves . . . Screening by medical history and physical examination alone would probably provide most of the same benefit without the risk." (4).

The BEIR estimate of six cases of breast cancer/1,000,000 women/rad/year is often quoted in estimating the risk of radiation-induced breast cancer. Such a relationship is suggested by the increased incidence of breast cancer found in survivors of the Hiroshima and Nagasaki bombings (6, 7). Similarly, Mettler found an increased incidence of breast cancer in women treated with radiotherapy for postpartum mastitis (6, 7). MacKenzie found an increased incidence of breast cancer in women who had repeated fluoroscopic examination to evaluate the treatment of pulmonary tuberculosis (6, 7). More recently, Simon reported 16 cases of breast cancer in women treated with radiotherapy for acne, or hirsutism, 25–50 years previously (7). The radiation exposure in these studies ranged from 90 rads in the Hiroshima bombings to 1000 rads in the women who received radiotherapy for the treatment of acne.

Swartz and Reichling point out the error in drawing conclusions from the large doses of radiation received by these patients (3). The dose-response relationship for carcinoma may not be linear. If this is so, the risk of cancer from the average two rad mammogram can not be extrapolated from the 1000 rads reported by Simon. In Bailar's analysis of breast carcinoma, a linear dose-response curve was, indeed, found (6). Furthermore, Bailar concluded that extrapolating from large doses of radiation would, if anything, underestimate the risk of cancer in lower doses. This is because of a flattening of the dose-response curve and a destructive effect on malignant cells at very high doses.

Mr. Grunfeld is a 4th-year student, Mount Sinai School of Medicine of The City University of New York, N.Y.

While the safety of mammography has been questioned, its accuracy has nonetheless been doubted. Pressman studied the effectiveness of mammography in the diagnosis of 100 cases of proven breast cancer (8). He found that there was no correct mammographic diagnosis in the two women who were 21–30 years old. The accuracy increased with age, so that breast cancer was diagnosed correctly 42% of the time in women 31–40 years of age, and 50% of the time in women 41–50 years of age. The accuracy for ages 51–60 and 61–70 were 63% and 72%, respectively.

Lesnick's series of 106 women under 45 years of age with proven breast carcinoma confirms these findings (9). Of the 52 women who had preoperative mammography, only 19 (37%) were diagnosed as suggestive of carcinoma. Furthermore, only two of the tumors were detected by mammography, while 84% of the masses were detected by the women themselves. Treatment was delayed in 29% of these 52 women because of false, negative mammograms. He concludes that if a patient has a palpable breast mass, a normal mammogram should be disregarded. However, the presence of unequivocable mammographic diagnosis of malignancy should supersede a normal physical examination.

A similar analysis was performed by Bross who measured the number of cases of breast cancer that passed undetected in screened women (10). He found screening for breast cancer by mammography is most effective in women older than 60 years of age. The number of cases of breast cancer that were detected by mammography exceeded the number that passed undetected in women 40–60 years of age. For women below the age of 40, the effectiveness of mammography as a screening procedure was negligible.

Despite the controversy, mammographic detection of cancer in older and high risk individuals is accepted by most authorities. High risk has been defined by Kalisher and Schaffer as those women with (11):

1) previous breast cancer: There is a 9% chance of developing a second primary cancer in ten years, a 2% chance of bilateral cancers on presentation, and 16% will eventually develop a second primary cancer.
2) a strong family history of breast cancer: Daughters of women with breast cancer demonstrate a three to four fold increase of incidence.
3) proliferative dysplasia of the breast: that is, papillomatosis and ductal hyperplasia.
4) first pregnancy after 35 years of age.
5) long duration of menstruation: menarche before 12 years of age and late menopause.
6) an ovarian or endometrial cancer.
7) a questionable correlation with exogenous hormone ingestion.

They recommend a baseline mammogram at age 35 years and annual mammograms after age 40 for this high risk group. They further define a symptomatic group as those women with a lump, a pain in the breast, or nipple discharge. Symptomatic women should have a mammogram, though it need not be repeated unless they are at high risk. The low risk group should have a baseline mammogram at age 40 to evaluate ductal patterns, a second mammogram one year following menopause, and then a mammogram every three to five years. The detection rate is raised from 2/1000 in the general population to 24/1000 by screening only high risk women.

In addition to screening high risk women, Peck and Lowman also recommend mammography be used (1):

1) preoperatively in all women with carcinomas of the breast to evaluate the lesion and to determine the presence of contralateral masses.
2) preoperatively in women over 35 years of age with clinically benign masses to search for unsuspected malignancy.
3) in women with a mass of uncertain nature.
4) in patients with lumpy breasts.
5) in women with large fatty breasts where palpation is difficult.
6) in cases where there is a bloody nipple discharge.
7) before chemotherapy or radiotherapy, as a baseline.
8) in a search for a primary tumor in a patient with axillary nodes.

Peck and Lowman also describe the limitations of mammography. They believe it to be of no value in:

1) patients with immature breasts.
2) patients with severely dysplastic breasts where there is poor correlation between palpable nodules and roentgen images.
3) uncooperative patients who cannot maintain their position for the 0.7-1.5 seconds needed for the study.
4) patients with a mass in the periphery of the breast.

Bailar is more cautious in his approach (6). He feels that only women at high risk warrant mammographic examination if they are younger than 50 years of age. In women younger than 35 years of age, Bailar believes that mammography should be used only as the step before biopsy. He further stipulates that mammography only be performed if it can be guaranteed that the equipment will deliver less than one rad.

Bailar's prospects for the future demand further development of our existing diagnostic techniques (6). He believes that dose reduction in mammography is essential. The amount of radiation is related to the type of recording material used. The standard Kodak AA film requires six to eight rads per exposure, while most newer techniques require less than one rad (12). The effectiveness of the new dose-reduced films was reported by Mintzer who found comparable accuracy with a skin dose of 0.8 rads (13). The records of sale of the dose-reduced films have shown a trend toward the use of these newer methods by radiologists (12).

Another attempt at dose reduction was reported by Cuker et al who found that the lateral view was sufficient, in most cases, to make a diagnosis of malignancy (14). The accuracy for the single view was 97%, comparing favorably to the 99% of the standard two-view technique. Applying only single lateral views to follow-up mammography would halve the radiation delivered to the patient.

As an alternative to mammography, thermography is available. Favorable results are reported by Dodd who claims 85% true positive results (12). Unfortunately, low rates of false positive interpretations are associated with increased false-negative results. This is because of the thermal response of benign lesions and the lack of thermal response in small malignant lesions. The method is least effective in detecting small, early malignant lesions. Thermography is effective in the detection of changing thermal patterns in young women, once baseline thermograms have been taken.

Ultrasonics is not, at present, an alternative to the other diagnostic techniques. It can differentiate cystic from solid lesions, once they have been located by physical examination. Unfortunately, it does not do well in picking up small masses. In order to define a mass smaller than 0.5 cm, thirty images must be recorded. The time required to do this makes the use of ultrasonics impractical (12).

Bailar points out the need for further research as we do not, at present, know the optimum interval for screening. One area to explore would be the risk of breast cancer based upon the appearance of the breast parenchyma on a single set of mammograms (6).

Summary

In conclusion, mammography is a powerful tool in the diagnosis of malignant lesions in older and high risk patients. Like all other tools in medicine, it must be used cautiously. It is of value only in those situations where important information can be gained without causing significant risk to the patient. For its effective use, the benefits must outweigh the potential hazards of the technique. There is the need for the development of better diagnostic techniques that will aid in the diagnosis of breast cancer without causing risk to the patient.

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The Perioperative Management of Patients with Pheochromocytoma

VASILIOS PRATILAS, M.D., MARGARET G. PRATILA, M.D., AND IVAN DIMICH, M.D.

Although pheochromocytoma was first described by Fraenkel (1) in 1886, the first successful operative removal of the tumor was performed by Charles Mayo (2) in 1927.

There was a 25%–45% mortality following surgery prior to 1950(3). Improvement in preoperative, operative and postoperative care has reduced mortality to ranges from 3% in uncomplicated cases to 20% in those that are complicated (4).

Pheochromocytoma is a relatively rare, most often histologically benign tumor of the sympathetic nervous system that secretes excessive quantities of epinephrine and/or N-epinephrine into the blood stream. Ninety percent of these tumors are in the adrenals (more often the right than the left). Eight percent are in chromaffin tissue within the abdomen and only 2% are located extra-abdominally in the thorax or neck (5). About ten percent are bilateral or multiple (this is common in children) and between six to ten percent are malignant (6).

Other neural crest tumors, such as ganglioneuromas and neuroblastomas may occasionally secrete catecholamines (7). Association with other diseases occurs, including cancer of the thyroid (Sipples Syndrome), neurofibromatoses, parathyroid adenomas and Von Hippel Lindau disease (8–11).

Physiology

Chromaffin cells produce catecholamines, three of which occur in the body; that is dopamine, norepinephrine and epinephrine. Norepinephrine (NE) is the neurohumoral transmitter of the adrenergic nervous system. Its main biosynthesis occurs within the postganglionic sympathetic neurons. Most NE is released intraneuronally and is converted by monamide oxidase to vanillylmandelic acid (VMA) and 3-methoxy - 4 hydroxyphenyl ethyleneglycol (HMPG). Nerve impulses cause the release of NE and following receptor cell response, NE diffuses throughout the body. Some passes to the local intraneuronal storage granules and some to the liver where normetanephrine is formed through the action of catechol-o-methyl-transference. Epinephrine is synthesized and stored in the adrenal medulla in a similar manner. Epinephrine is released into the circulation by preganglionic stimulation or by biochemical states such as hypoglycemia. Dopamine is found as an end product in parts of the brain, liver, intestine, and lungs. In nervous tissue, dopamine is found in the cytoplasm and forms, at most, 50% of the total tissue catecholamines. Its breakdown products are 3 methoxy-tyramine (COMT catalyzed) and homovanillic acid (MAO catalyzed) (Fig. 1).

The derangements seen in pheochromocytoma are accounted for by the known physiologic effects of epinephrine and norepinephrine that include hypertension, alterations in pulse rate, and hypermetabolic state.

Hypertension. Severe hypertensive cardiovascular disease can be produced by pheochromocytomas. Convulsions can occur from hypertensive encephalopathy. Hypertension can be sustained or paroxysmal. In patients with sustained hypertension, episodes of generalized sweating, vasomotor disturbance, and accentuation of their basal hypertension may occur. This is the common symptom in children in whom impaired growth is often a striking feature (12). If treatment is not instituted, visual impairment and congestive heart failure may occur. In patients, paroxysmal hypertension attacks may be accompanied by feelings of great anxiety, palpitations, pallor, headache and sweating. A few patients remain normotensive and have no attacks but the stress of surgery or parturition will suddenly liberate enormous amounts of catecholamines from their tumors with resultant severely high blood pressure or cardiac arrest.

Alterations in pulse rate. The catecholamines have characteristic effects on the pulse. N-epinephrine causes bradycardia while epinephrine produces tachycardia that may be excessive. Most extra-adrenal pheocromocytomas secrete N-epinephrine but Mannix et al have re-

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From the Department of Anesthesiology, Mount Sinai School of Medicine, CUNY, New York, N.Y.

Request for reprints should be sent to V. Pratilas, M.D., One E. 100th Street, New York, N.Y. 10029.

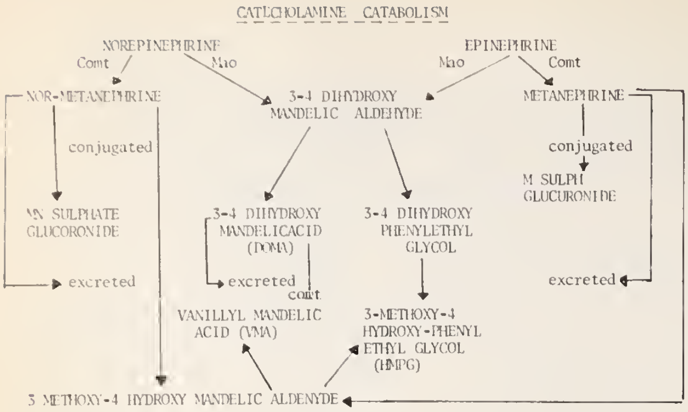
CATECHOLAMINE CATABOLISM
NOREPINEPHRINE
Comt
Mao
EPINEPHRINE
Mao
Comt
NOR-METANEPHRINE
3-4 DIHYDROXY MANDELIC ALDEHYDE
METANEPHRINE
conjugated
conjugated
M SULPH GLUCURONIDE
MN SULPHATE GLUCORONIDE
3-4 DIHYDROXY MANDELICACID (DOMA)
3-4 DIHYDROXY PHENYLETHYL GLYCOL
excreted
excreted
excreted
comt
VANILLYL MANDELIC ACID (VMA)
3-METHOXY-4 HYDROXY-PHENYL ETHYL GLYCOL (HMPG)
3 METHOXY-4 HYDROXY MANDELIC ALDEHYDE

FIG. 1.

ported epinephrine production in a tumor arising from one of the lumbar (L) sympathetic ganglia (13).

Hypermetabolic state. When produced by the catecholamines this can be mistaken for thyrotoxic or an anxiety state. Epinephrine, and to a lesser extent norepinephrine, causes glycogenolysis, hyperglycemia and glycosuria. Wilber and his co-workers (14) have shown in a patient with pheochromocytoma that pancreatic insulin release was almost totally blocked but this inhibition was absent after surgical removal of the pheochromocytoma. Excessive sweating is also a frequently noted symptom in this disease.

Gastrointestinal hemorrhage (15), ileal infarction and ileus (16), have been reported, probably as a result of vascular changes associated with intense vasoconstriction.

Gupta (17) has reported an increased incidence of myocardial infarction associated with pheochromocytoma, possibly as a result of sudden beta receptor stimulation since it appears more frequently in those who do not have sustained hypertension.

Diagnosis

This cannot be made on the basis of symptoms alone. Similar symptoms may be found in anxiety states, hyperventilation syndrome, paroxysmal tachycardia, migraine headache, periodic cerebrovascular insufficiency, hyperthyroidism, menopause and others (18). Urinary metabolites should be measured in all patients that exhibit (19): 1) Hypertension. 2) Paroxysmal symptomatology. 3) Unexplained hypermetabolic state. 4) Inappropriate cardiovascular response to trauma, parturition, anesthesia. 5) Neurocutaneous syndrome. 6) Familial history of pheochromocytoma. 7) Multiple endocrine neoplasia—type II.

Probably less than 0.5% of patients suffering from hypertension have a pheochromocytoma (20). The diagnosis is based mainly on laboratory findings. Spectrophotometric assays for vanillylmandelic (VMA) have customarily been used for the detection of pheochromocytoma. They have been criticized as being unreliable mainly because of difficulties in obtaining a true 24-hour sample of urine.

Excretion of VMA is also studied by bidirectional paper or gas-liquid chromatographic methods and varies from 0.2 to 3.5 μg/mg creatinine in normal subjects (20). This requires only a random urine specimen and is not influenced by the most commonly used drugs or by diet as are the spectrophotometric techniques (21). In the absence of coma or a tumor of neural crest origin, VMA excretion in excess of 5 μg/mg creatinine is extremely rare (22).

Measurement of total metanephrines (TM) can be performed using a reliable photometric method (22, 23). Gitlow et al (20) have reported TM excretions of greater than 2.2 μg/mg creatinine in 107 subjects who proved surgically to have a pheochromocytoma. They state, however, that severe stress from conditions such as shock, congestive cardiac failure, severe sepsis, respiratory insufficiency and disseminated metastatic disease may also result in elevation of TM excretion. VMA excretion is, however, usually normal in these patients.

Pertsemlides et al (24) have stated that excretion by a noncomatose patient of excessive quantities of two catecholamine metabolites in separate urine specimens is diagnostic for pheochromocytoma.

Extreme increase in homovanillic acid (HVA) excretion in an adult indicates the presence of a malignant neural crest lesion (25). Normal levels do not, however, exclude malignancy as the majority of tumors are not associated with increased levels of this dopamine catabolite.

Pharmacologic Tests

Pressor tests are rarely used except when there is only intermittent functioning of the tumor. Histamine (26), glucagon (27), and tyramine (28) have been used but are not without risk to the patient. Severe bronchospasm may occur with histamine, while with all pressor tests disastrous hypertensive crises have occurred. Phentolamine has been used in the presence of sustained hypertension.

Gitlow (20) has described a more successful technique in patients with borderline increases in catecholamine catabolite excretion. The patient is observed over a period of months and periodic urinary catabolite determinations are made.

Radiologic Investigations

These are used most often to localize the tumor in a patient with known pheochromocytoma, diagnosed by other methods, but unsuspected tumors are sometimes diagnosed during the radiologic investigation of hypertension. X-rays of the chest (to exclude a mediastinal tumor) and abdomen, or IVP may show a tumor or renal displacement. The latter also confirms the presence of bilateral renal function. This is important as surgical removal may, on occasion, entail nephrectomy. Retroperitoneal pneumography (now outmoded) and angiography carry a higher risk. Translumbar aortography has produced massive retroperitoneal hemorrhage and has no place in the management of these patients. Since pheochromocytoma is a vascular tumor, retrograde aortic catheterization via the femoral artery is a worthwhile investigation provided patients are adequately monitored. Because of the technical difficulties associated with reexploration of the abdomen, patients with recurrent tumor may be best assessed by selective venous sampling for catecholamine assays and selective angiography (20).

Treatment

Because there is a high incidence of malignancy in these tumors, treatment must be surgical but only after adequate medical stabilization.

A complicating metastatic neoplasm or pregnancy are the only reasons to delay early surgery. As Gitlow et al (20) have stated, when no contraindication to surgery exists, the rule for preoperative management is that the patient should undergo no unnecessary tests or manipulations. Treatment may be planned for three phases-preoperative, intraoperative, and postoperative.

Preoperative

In the preoperative stage (Table I), Alpha receptor blockade has improved the management of these patients (29). There are two drugs in common usage. Phenoxybenzamine is a potent alpha adrenergic receptor blocking agent that can be given orally or intravenously. It is long-acting, with a half life of over 24 hours. The initial adult dose is 20 mg/day, orally. Ten mg/day increments are given to a dose just below that producing orthostatic hypotension.

The second drug of choice is Pentolamine HC1, a short acting α-blocker. We prefer to use this agent if surgery is scheduled because it obviates the prolonged alpha adrenergic blockade produced by phenoxybenzamine which might mask the presence of a second tumor. If phentolamine alone is used, the presence of another tumor would be evidenced by the rise in blood pressure within five minutes of its cessation. Phentolamine is prepared by diluting 5–10 mg in 500 ml of 5% D/W. The infusion rate required for adequate adrenolytic protection may vary from 2–60 mg/hr (or 30–1000 μg/min) (24).

The advantages of α-blockade are many. The patient feels better. Blood sugar levels are controlled. Not only is there competition for N-epinephrine and epinephrine sensitive receptors, but alpha receptor blockade allows reestablishment of a normal blood volume in patients who have contracted volumes due to α-adrenergic stimulation by the catecholamines. Serial hematocrits will show whether plasma volume is expanding at a greater rate than red cell production. This can be corrected by packed cells or whole blood if anemia occurs.

Beta adrenergic blockers have been used in the preoperative and operative period by many authors (30–36). These authors state that the β-blocking agents protect against dysrhythmias and permit reduction of the amount of α-blocking drugs necessary to control blood pressure (32). Beta blockade has also been suggested where tachyphilaxis to α-adrenergic blocking agents has occurred (33). Beta adrenergic blockade should be used only when α-blockade is established. Beta blockade, alone, may cause a marked rise in the total peripheral resistance due to vasoconstriction secondary to unopposed α-adrenergic activity (34).

The use of β-blocking agents is not without risk and recent reports have emphasized the problems of abrupt withdrawal (37). We reserve the β-blocking agents to two

TABLE I

Preoperative Drugs

Drug	Dose	Effect
Phenoxybenzamine	20 mg/day p.o. (Max. 160 mg/day) Given to 10 mg below dose producing orthostatic hypotension	α-adrenergic blockade Long acting
Phentolamine	Dilute 5-10 mg in 500 ml D5W i.v. 2-60 mg/hr (30/1000μg/min)	α-adrenergic blockade Short acting
Chlorpromazine	50 mg q 6/hr. p.o. 3 preop. days	Adrenergic blocking Antidysrhythmic Sedative
Propranolol	10-40 mg p.o. t.i.d.	β-adrenergic blockade Only to control dysrhythmia or sinus tach. (prior α blockade)
α-methylparatyrosine	1.5-3 g/day p.o.	Prevents catecholamine synthesis Parkinsonism

circumstances in the preoperative management of pheochromocytoma. They are used when there are frequent ventricular dysrhythmias and are used in cases of sustained tachycardia, generally in the range of 140/mm in the adult.

Alpha methyl paratyrosine has been said to cause substantial reduction in catecholamine synthesis (38). Smith et al (39) found, that despite a fall in urinary metanephine excretion, the patient had hypertension and tachycardia during induction of anesthesia, but dysrhythmia did not occur. Desmonts et al (40) and Jones et al (41) also have not found it to be completely satisfactory. It is given orally 1.5 to 3 gm/day. A side effect of the drug is the onset of symptoms resembling Parkinsonism. These are partially relieved by diphenhydramine.

Other authors have advocated the use of chlorpromazine in the preoperative preparation of the patient. They feel suppression of sympathoadrenal activity by α and β adrenergic blockade, deprives the cardiovascular system of an important homeostatic mechanism and use chlorpromazine to curtail the amounts of these agents. Chlorpromazine has adrenergic blocking, antidysrhythmic, and sedative properties (42).

A seemingly minor but important point in preoperative management is the avoidance of enemata. These may produce a severe hypertensive crisis.

Premedication

Nearly all the commonly used premedicant drugs have been used successfully in the management of patients with pheochromocytoma (Table II). Edelist (43) has suggested the use of an antihistamine to counteract the effects of drugs that may release histamine. Theoretically, narcotic analgesics may excite tumor activity through histamine-like effects or respiratory depression. Atropine (44) is omitted by most, but not all, authors (47) as tachycardia may occur.

Intraoperative

Anesthetic management of the patient undergoing surgical removal of a pheochromocytoma is directed toward control of the cardiovascular system.

Close monitoring is an absolute necessity and includes EKG, CVP, continuous arterial pressure readings and a Swan-Ganz catheter (45). Preoperative excess catecholamine output leads to chronically constricted blood volume. Preoperative rehydration is an essential part of the preoperative preparation of the patient. Measurement of pulmonary capillary wedge pressure helps in correctly assessing intravascular volume replacement. Again, during surgery, enormous swings in blood pressure can occur. Changes in vascular resistance can be rapidly detected and appropriate therapy instituted.

Sodium thiopenthal has been used as the induction agent in almost every case of pheochromocytoma in which surgery has been performed.

Virtually all inhalation anesthetic agents have been used for the maintenance of an adequate depth of anesthesia during the removal of a pheochromocytoma. Uncontrolled hypertension, severe hypotension and cardiac dysrhythmia are the most serious problems encountered. While hypertension may occur during manipulation of the tumor or during transfer to the operating table (increased intra-abdominal pressure), coughing during intubation or during the surgical preparation also may precipitate catecholamine release and severe hypertension (46). A sufficient depth of anesthesia is obviously necessary during all these maneuvers.

Severe hypotension following tumor removal is rare since alpha blocking agents have been used preoperatively and adequate fluid replaced.

Propranolol is used in the treatment of dysrhythmias but may slow recovery of cardiovascular stability in the postoperative period. Most authors prefer to use intravenous lidocaine. The Mount Sinai group has found increasing the depth of halothane anesthesia to be effective (22).

Gould and Peny (47) reported on Mayo Clinic results of patients anesthetized with diethyl ether. Although diethyl ether allegedly liberates catecholamines (48), tachycardia and cardiac dysrhythmias were not a major problem when diethyl ether was the primary agent.

Halothane, methoxyflurane, and enflurane all depress the spontaneous release of catecholamines from the adrenal medulla and the secretion evoked by splanchnic-nerve stimulation (49, 53, 54). Enflurane, methoxyflurane and fluroxene do not sensitize the heart to catecholamine induced dysrhythmias (52). Only the halogenated hydrocarbon, halothane lowered the dysrhythmic threshold doses for epinephrine. These findings have supported previous studies (53). Reynolds et al (54), in studies using intracellular microelectrode techniques, showed that the main effect of halothane in cardiac conducting fibers is a slowing of conduction. This is due mainly to a decrease in the rate of phase 4 depolarization of the action potential. This is characteristic of an antidysrhythmic agent. Reynolds and Chiz (55) also showed that epinephrine markedly potentiated the modest slowing of conduction produced by halothane. This effect was antagonized by α-adrenergic block but not β-adrenergic block. It is widely believed that decreased velocity of conduction is conducive to the production of cardiac dysrhythmias of the reentrant variety (56). Zink et al (57) and Hashimoto (58) published work that supports this view. In Zink's work, a critical level of blood pressure and atrial rate were necessary for induction of dysrhythmia. Methoxyflurane was shown to have a depressant effect on the primary pacemaker with secondary pacemaker stimula-

TABLE II

Premedication (Adult)

Drug	Dose mg (i.m.)	Effect
Barbiturates		
Pentobarbital	75–100	Resets HR at higher value per given BP
Secobarbital	75–100	Useful, little CV action at normal doseage
Narcotics		
Morphine	5–15	Causes catecholamine release
Meperidine	50–100	Direct action on vasc. smooth muscle May have hypotension
Diazepam	5–10	Antidysrhythmic
Droperidol	2.5–5	α-adrenergic receptor block or loc. anes. effect. Antidysrhythmic. Occ. severe hypertension (cause?)
Atropine	0.4	Vagolytic. Results in tachycardia, AV dis. Nodal & vent. premature contraction

tion (54). This favors a shift of pacemaker activity to the ventricular conducting system and results in a dysrhythmia originating in an ectopic focus. Clinically, however, dysrhythmias are less likely to occur with methoxyflurane and it has been used widely as anesthesia for the removal of pheochromocytoma (31). Only its renal toxicity now precludes its use. Dysrhythmias that occurred during halothane anesthesia have been treated by increasing the concentration of halothane so the situation remains far from clear.

Enflurane has been used for the removal of pheochromocytoma in recent years (44). Reports have shown a decreased incidence of dysrhythmia during surgery. Kopriva and Eltringham (59) reported only nodal premature contractions during manipulation of the adrenal gland. Kreul et al (60) have shown that ventricular dysrhythmias did not occur despite levels of circulating catecholamines that were ten times normal. Johnston and Elger (61) reported the arrhythmic threshold for epinephrine injected subcutaneously to be 7.5 μg/kg. Kreul et al believed their patients had circulating catecholamine levels that exceeded this dosage. Their explanation for the lack of dysrhythmias was a tolerance of tissue receptors to circulating catecholamines in patients with pheochromocytoma. This would certainly seem possible in view of the mechanism of dysrhythmia formation discussed above.

Kumar and Zsigmond (62) recently reported their experiences with 34 patients with pheochromocytoma over an 11-year period. Two deaths that occurred in their series were the result of acute myocardial failure following a prolonged period of severe hypertension. They believe vasopressor therapy to be dangerous in these circumstances as the failure may be caused by active catecholamine myocarditis (63). They suggest the use of mechanical circulatory assistance with an aortic balloon pump to permit the myocardium to recover. The use of the aortic balloon assist to treat patients who are unresponsive to drug therapy has been suggested by Curtis, et al (64).

Many authors have reported favorably on the use of neuroleptanesthesia using a combination of droperidol and fentanyl for removal of pheochromocytomas (40, 65, 66). Droperidol antagonizes the pressor effects of the catecholamines and prevents dysrhythmia (67) either by alpha blockade (68) or local anesthetic action (69), while fentanyl has been shown to have an alpha-adrenergic-blocking effect (70). Sumikawa (71) and Amakata described a marked increase in blood pressure following droperidol administration in such a patient. They postulate this could be from central stimulation of the sympathoadrenal system, from direct stimulation of the tumor cells or sympathetic nerve endings, from the evoked release of catecholamines, from a positive feedback system due to the initial hypotension or, that droperidol may inhibit the uptake of catecholamines into the nerve terminals.

Neuromuscular-blocking agents used for surgery for pheochromocytoma have included succinyl dicholine, d-tubo-curare and pancuronium (Table III). Gallamine (72) has been generally avoided because of its anticholinergic action. Brown and Crout (73) believe it has a direct beta adrenergic stimulant effect on the cardiac receptors. Galindo and Davis (74) proved that succinyl choline lowers the threshold of cardiac excitability. They attribute this to sympathetic postganglionic stimulation with a direct myocardial effect. Mathias and Evans-Prosser (75) demonstrated that small amounts of d-tubocurare block the succinyl choline induced dysrhythmia. Katz and Bigger (76) believe this is because of its ganglion-blocking property. Tumor activity may be excited by d-tubo-curare through its ability to liberate histamine. Clinically, however, both succinyl choline and tubocurare have been used successfully. Pancuronium does not release histamine (77) and has no ganglion blocking effect in man (78). No appreciable changes in levels of catecholamines have been observed following pancuronium.

Both lidocaine and beta adrenergic-blocking agents have been used for the treatment of dysrhythmia during surgery for pheochromocytomas (Table IV). They are

TABLE III

Muscle Relaxants

Drug	Effect	Dysrhythmia	Blood Pressure
Succinylcholine	↓ cardiac excitability threshold Sympathetic post-ganglionic stimulation	Bradycardia Sinus arrest Supraventricular & ventricular	Elevated
d-tubo-curare	Ganglionic blockade Prevents SDC produced dysrhythmias		Releases histramine (tumor activity may be excited) Large doses-ganglion blockade may cause ↓ BP
Pancuronium	No stimulation of tumor activity No ganglion blockade or histamine release	Vagolytic May have tachycardia	Elevated
Gallamine	Anticholinergic ? β-adrenergic stimulant	Tachycardia	Elevated

TABLE IV

Intraoperative Drugs

Drug	Dose	Effect
Pentolamine HCI	Dilute 25-50 mg in 500 ml D5W 10-300 mg/hr (150-5000 μg/min)	α-adrenergic blockade Short acting Control of BP
Nitroprusside	0.5-1.5 μg/kg min. Total dose not to exceed 3-3.5 mg/kg (or 1 mg/kg?)	Direct act on smooth muscle wall vessel. Very short acting Generally ↑ HR & ↓ BP
Propranolol	1-2 mg i.v. bolus (5 mg maximum)	β-adrenergic receptor blockade Only to control dysrhythmia or sinus tach.
Lidocaine	1 mg/kg i.v. bolus	↑ K^+ conductance membrane. Effective against reentry dysrhythmias

both effective, although their mode of action probably differs. The action of lidocaine has been described as increasing membrane conductance for potassium (79). This would effectively eliminate dysrhythmias produced by the reentrant phenomenon. Other authors have contradicted these findings. They believe lidocaine acts like other local anesthetics by decreasing the inward sodium current (80). Rosen et al (81) suggest lidocaine can slow conduction through its effect on phase 0 depolarization and membrane responsiveness.

Propranolol appears to antagonize directly the cardiac adrenergic stimulating activity of catecholamines (82). However, a nonspecific depressant effect similar to that of lidocaine also occurs and this may be of importance in its use in the treatment of dysrhythmias (83).

Phentolamine is the drug most often used for management of the hypertensive episodes during the stress of anesthesia and surgery. Generally, approximately five times the preoperative dose is needed during the critical phases of surgery such as endotracheal intubation and tumor manipulation.

Sodium nitroprusside has been used intraoperatively for treatment of hypertension. Its action is immediate and directly on the vessel wall. Recovery occurs in one to two minutes. Stamenkovic (65) has suggested discontinuing the nitroprusside one minute before ligation of the venous drainage from the tumor, as hypotension commonly occurs with cessation of catechol liberation from the tumor into the circulation. He emphasizes the value of nitroprusside as no ganglion blocking agents, vasopressors or antidysrhythmic drugs were required in patients treated with nitroprusside. Csanky-Treels et al (84) have reported a case in which the rapid onset and cessation of action of nitroprusside enabled the diagnosis of further tumors to be diagnosed intraoperatively.

Following removal of the pheochromocytoma, falls in circulatory catecholamine level may result in hypotension. Rapid infusion of Ringer's Lactate and/or blood are the treatment of choice with careful cardiovascular monitoring. If vasopressors are needed, L-norepinephrine is favored by most authors (32, 85).

Postoperative Management

Close monitoring is mandatory during the immediate postoperative period. Adequate urinary output is of far more importance than the level of the blood pressure itself.

Hypotension, tachycardia, and decreased urinary output may indicate–inadequate correction of the blood volume deficit, an acute medical problem such as myocardial infarction, cardiac failure, sepsis or retroperitoneal bleeding.

Special Situations of Importance to an Anesthesiologist

Patients with pheochromocytoma may remain asymptomatic until they have an operation. Such a patient may develop severe hypertension and tachycardia intraoperatively or in the early postoperative period. Symptoms may progress eventually to unconsciousness, dyspnea, and collapse. A myocardial infarct may be suspected in these cases. Death may ensue without treatment (86). Death has also resulted from trauma, pregnancy and delivery.

Schenker and Chowers (87) reviewed cases of pheochromocytoma associated with pregnancy. In these cases when diagnosis was not made prior to delivery, maternal mortality was 58% and fetal mortality was 55%. Antepartum diagnosis reduced maternal mortality to 18% with a fetal mortality of 50%.

Several recent publications have reported on favorable outcomes of pregnancy in patients where pheochromocytoma was diagnosed during pregnancy (88). Symptoms were controlled in one patient with phenoxybenzamine and both were treated by stimultaneous cesarean section and excision of the pheochromocytoma. Neurolept anesthesia and d-tubocurare were used in both patients for maintenance of anesthesia, following induction with sodium thiopental and succinyl choline. Both patients developed symptoms late in pregnancy at the 7th month. Another patient (89) who developed symptoms at the end of the second month of pregnancy did not have such a happy outcome. In spite of phenoxybenzamine treatment, she had spontaneous rupture of membranes accompanied by a hypertensive crisis and delivery of a child that died shortly after birth.

In this review we have documented the preoperative, intraoperative (as related to anesthesia) and postoperative management of patients with a pheochromocytoma. At each phase, advances in the management of these patients, coupled with improvement in diagnosis, have contributed to the great decrease in mortality which has occurred since the 1950s. Treatment remains surgical, because of the high incidence of malignancy. Anesthetic management of patients with pheochromocytoma entails close monitoring in the operative and early postoperative period. Nearly all anesthetic agents have been used successfully during operations for the removal of pheochromocytomas. Their individual pharmacology, especially in relation to hypertension and dysrhythmias, has been discussed.

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Ambulatory Surgery: Experience with Two Thousand Patients

ROBERT A. NABATOFF, M.D. AND ARTHUR H. AUFSES, M.D.

During the past decade there has been an ever-increasing interest in ambulatory surgery. Since 1971 ambulatory surgical procedures have been carried out on a progressively larger scale at Mount Sinai School of Medicine. Stripping operations for varicose veins, hernioplasties and many other diverse procedures are now being done under general anesthesia in this fashion. Although the patients studied in this report had varicose vein surgery, the operative routine and patient management would be applicable to any type of ambulatory surgery. This report describes the technique which has gradually evolved and the clinical results.

Preoperative Management

When the patient is informed that his operation can be performed on an ambulatory basis, there is practically always an enthusiastic reaction. Many say they didn't come for surgery sooner because they believed it involved a prolonged hospital stay. They are delighted to know they can return to work on the first or second postoperative day. All instructions are given in printed form when arrangements are made for surgery. A thorough medical check-up is recommended. One week before admission, the patient reports to the hospital laboratory for routine diagnostic tests. Up to the age of 35, a urinalysis, blood count and 12-channel blood study are required. Over the age of 35, an electrocardiogram and x-ray of the chest are also mandatory. If a patient lives far from the hospital, these tests can be performed locally in his physician's office or at a reputable laboratory. The results of the laboratory tests are forwarded to the ambulatory room so that they are available when the patient reports for surgery.

The patient is advised to remain normally active until the time of admission. He shaves the operative area the night before surgery and takes nothing by mouth after midnight. The morning of surgery he reports to the ambulatory admitting office at 7 a.m. and is then taken to the ambulatory room. Blood pressure, temperature and other vital signs are checked and the patient is examined by an anesthetist, who also reviews the laboratory results. No preoperative medication is usually given.

Operative Procedure

Surgery is scheduled at 8 a.m. or as soon thereafter as possible. Although the depth of anesthesia must be sufficient to provide optimal operating conditions, a light plane is mandatory so that the patient can walk several hours following operation. Spinal anesthesia is undesirable because the patient is unable to walk within a few hours following surgery. An effective technique has been developed by Dr. David Stark and his associates at Mount Sinai. It provides a smooth induction and a tranquil emergence from anesthesia. The requirements for this type of ambulatory surgery have been met very well by the use of a barbiturate-nitrous-oxide-halothane sequence. The patient is awake almost immediately following surgery. Intubation has been used without hesitation if circumstances demand it. The electrocardiogram, blood pressure and axillary temperature are monitored in the usual way.

Special attention to hemostasis and surgical details is essential to avoid complications after discharge from the hospital. The operative procedure should be performed expeditiously to minimize operating time. The less time on the operating table under anesthesia, the sooner a patient can become ambulatory and be discharged. The dressings are applied securely so that they remain intact even though the patient is carrying out all of his normal activities.

Only aspirin or Tylenol^{R} are given, when necessary during the immediate postoperative course. If stronger analgesics are used, the patient will be unable to walk and go home that same day. There is no contraindication to the use of stronger analgesics or medication for sleep

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From the Department of Surgery, Mount Sinai School of Medicine of The City University of New York, New York, N.Y. 10029.

once the patient has returned home. Although there is usually some discomfort when the anesthesia wears off, it usually improves once the patient becomes ambulatory. Most patients feel well enough to eat lunch. About two to three hours postoperatively the patient walks with assistance. He then returns to bed and rests until about 2 p.m. At that time he tries to walk by himself. He can be discharged only after walking on his own for one hour. No patient is permitted to leave the hospital unless someone is available to take him home. Almost all of the patients have been discharged between 2 p.m. and 4 p.m. If they are unable to walk by that time they are advised to wait another hour or two until the residual effects of the anesthesia have disappeared. All patients have been able to go home on the day of surgery. The patient is informed about problems that might be encountered at home and is advised to call if anything unusual occurs. He is instructed to avoid disturbing or wetting the bandages. If there is unusual discomfort, Anacin^R or Darvon^R is usually sufficient. Most patients do not require any medication, especially if they are fully active. They are advised to go to bed after arriving home from the hospital but to return to normal activity the following morning.

Postoperative Course

There have been no significant problems encountered following discharge from the hospital. The fact that no preoperative medication is given has resulted in a great decrease of postoperative sequelae, such as nausea, dizziness and vomiting. Those patients who returned to work the day following surgery had the fewest problems. If they live nearby and it is convenient, they are instructed to come to the office on the first or second postoperative day for reassurance, to check the bandages and to make sure they are fully active. If this is not feasible, they need only come at the appropriate time for suture removal. Normal physical activity seems to decrease the amount of pain. Patients were most uncomfortable upon arising in the morning, after a night in bed. Sutures were removed at the usual time following surgery. There were no problems with wound healing. If anything, healing seemed better than usual. There were no instances of wound separation despite vigorous physical activity shortly following operation. There were no significant hematomas or any other indications of unusual bleeding. No wound infections occurred in this series.

Thrombophlebitis and Pulmonary Embolism

Despite extensive research the incidence of peripheral phlebitis and embolization in the postoperative patient has not changed during the past decade. One to two percent of all surgical patients develop phlebitis postoperatively and 0.5 percent experience pulmonary emboli (2). Although the exact mechanism for the development of thromboembolic phenomena remains obscure, such factors as platelet adhesiveness, stasis resulting from inactivity and dehydration may all be incriminating factors. Early ambulation has long been recognized as a vital factor in minimizing these complications. In this series of 2,000 cases, there were no instances of phlebitis or embolism. It is probably the abrupt change of normal body function and activity that makes a patient susceptible to thromboembolic phenomena. With this ambulatory technique there is very little disruption of normal activity.

Discussion

Since the advent of ambulatory surgery there has been a great saving of hospital beds and a significant decrease in the work-load of hospital personnel. No one has to shave the operative area or transport the ambulatory patient to the operating room. Since the patient is not immobilized, preoperative enemas and postoperative catheterizations are not required. The patient does not have to be seen by the surgical resident since his physical examination is carried out before hospital admission. There is substantial financial benefit for the patient since he can return to gainful employment shortly following surgery. Considerable savings also accrue to the hospital and providers of health insurance. At the onset, there was considerable reluctance on the part of insurance companies to pay hospital expenses for ambulatory patients. For many years, Blue Cross would provide payment for hospital bills only if the patient stayed overnight. This is gradually changing since all parties involved are now realizing substantial savings as a result of ambulatory care.

The patient response to ambulatory surgery has been uniformly favorable. Only rarely does someone express a preference to stay in the hospital overnight. If the patient insists, orders are given to make certain that he is ambulatory several hours following surgery and discharged the morning following surgery, at the latest. If the patient expresses a desire to extend his hospital stay even further, he is informed that additional hospitalization would be of no value and would increase the risk of postoperative complications. No other persuasion is usually necessary.

Summary

During the past eight years, a series of 2,000 patients have had surgery performed under general anesthesia on a fully ambulatory basis. The patients enter the hospital at 7 a.m. and leave between 2 to 3 p.m. No significant problems have been encountered. Since this technique provides for a great saving of hospital beds, minimizes complications, and is accepted enthusiastically by patients, it is hoped that an ever-increasing number of diverse operative procedures will be performed in this manner.

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Organizing Library Audiovisual Services to Support Continuing Education*

MERRIL K. SCHINDLER, M.L.S., RACHAEL K. GOLDSTEIN, M.S., AND JANE PORT, M.S.

Abstract

The Levy Library of Mount Sinai School of Medicine has been supported by the National Library of Medicine in an effort to identify and develop a program that meets the special needs of health sciences professionals engaging in continuing education. This paper describes the background, planning, and activities of the first 18 months of the Library Mobilization for Continuous Education Project.

Background

Since its inception, Mount Sinai School of Medicine has utilized audiovisuals (AVs) as integral elements of its teaching program, and the multidisciplinary laboratories for first- and second-year medical students were designed to enable faculty to incorporate AVs into their laboratory teaching (1).

Library services at Mount Sinai date from the 1906 establishment of the Jacobi Library. To supplement this clinical collection, the Basic Sciences Branch Library was opened in 1968 when the first class of medical students was admitted (2). Neither of these facilities was able to accommodate AV service, and the library had no part in its provision. Self-instructional AV programs and equipment for first- and second-year students were managed, housed, and used in the multidisciplinary laboratories; other students and staff at Mount Sinai had no access to AV materials. In July 1974, when the two libraries merged and moved into new quarters, the newly formed Gustave L. and Janet W. Levy Library undertook the responsibility for providing AV service to all segments of the Mount Sinai population. Curriculum-related, self-instructional AV programs and some playback equipment were transferred from the multidisciplinary laboratories, and the library began a highly selective program of AV acquisitions for its general collection. AV programs and portable playback equipment were housed behind the circulation desk with the reserve book collection and could be accessed only through the card catalog. Each item had to be requested and charged out for use in the library as well as for use off the premises. While this AV service met the major needs of the undergraduate medical curriculum with its large component of specifically assigned programs, it was inadequate for less structured learning purposes, including continuing education (CE).

Mount Sinai's long history of CE activity dates from courses offered in 1910. MSSM's Page and William Black Post-Graduate School of Medicine was founded in 1967. Ten years later it became part of the Brookdale Center for Continuous Education which encompasses all of Mount Sinai's CE programs for physicians, social workers, nurses, allied health personnel and consumers/patients. In 1977/78, the Brookdale Center offered over 100 courses for physicians and allied health personnel, drawing over 4000 students from across the United States and from other countries, as well as from the New York region. Approximately 90% of the instructors were members of the MSSM faculty. The Center projects further increases in course enrollment as continuing education burgeons in response to the efforts of professional associations and in anticipation of possible future mandatory relicensure.

A search of the literature revealed that little has been reported on the analysis of library needs of health sciences CE participants or on library provision of materials to support formal CE programs. Our own experience indicated that, based on their limited use of library resources, CE course participants at Mount Sinai did not consider the library as an integral part of this educational experience. There are other respects in which CE programs differ from education for the M.D. and Ph.D.:

—A CE course is usually a concentrated exposition dealing only with the latest techniques or developments on an extremely circumscribed topic.

From the Gustave L. and Janet W. Levy Library and the Department of Medical Education, Mount Sinai School of Medicine of The City University of New York, NY 10029.

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Requests for reprints should be sent to: Merril K. Schindler, Gustave L. and Janet W. Levy Library, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029.

—CE courses draw participants from a wide geographic area and many attendees are unfamiliar with local library resources.

—CE courses are frequently of short duration, sometimes lasting one day or less, thus limiting opportunities for participants to visit the library.

—CE course participants do not generally regard themselves, nor are they regarded by their instructors, as "students"; they are colleagues.

—CE participants regard reading lists as personal files for future reference rather than as assignments to be completed immediately.

Planning the Project

In 1975, the administrators of the Levy Library and of the Page and William Black Post-Graduate School of Medicine began to explore ways to offer library service to CE participants and instructors. This cooperative effort was the result of:

—Recognition that the library gave no formal support to this major institutional program.

—Recommendations made by a task force charged by the Mount Sinai Board of Trustees to develop long range goals, advocating the strengthening of CE programs and requirements at Mount Sinai.

—The apparent potential for future rapid growth of CE nationally in response to increasingly rigorous professional standards (3).

—The perceived need for developing a model of service that could be usable in other settings.

—A shared interest by Mount Sinai's library and CE directors in researching how library requirements of continuing education programs differ from those of undergraduate medical education.

It was agreed that needs of the Post-Graduate School faculty for literature and AV materials to assist them in course planning and presentation had not been systematically addressed. Furthermore, participants' course evaluation forms had, for several years, consistently indicated a desire for high quality follow-up materials and for continuing studies beyond the limitation of the courses themselves. With all this in mind, a grant request was developed and submitted to the National Library of Medicine. The project proposed to investigate CE course participants' needs and to develop alternate strategies for identifying, acquiring and determining the best means of distributing appropriate materials to them. The major objective was establishing an active program of educational outreach based on a collection of print and nonprint materials carefully selected by library and other faculty for the following user groups with related interests: post-graduate school faculty preparing courses, participants in these courses, house staff, attending physicians, and other health practitioners at Mount Sinai and its affiliated hospitals. Project staff would also work with the post-graduate faculty to develop subject packages of print and nonprint materials geared to the content of specific courses. The library would then promote use of these materials and publicize each subject package through exhibits, memos, and posters at Mount Sinai and its affiliated hospitals. Bibliographies of materials in these multimedia packages would be distributed widely at MSSM and to other libraries. Providing this assistance to the Post-Graduate School faculty and students would simultaneously extend the school's reach and maximize utilization of library materials by individuals who were not formally registered in the courses.

Early Project Activities

With approval of the proposal and the availability of funding in January 1977, the first activity of the newly hired Project/AV Librarian and clerical support staff was to build an AV reference and program collection. Experience during the first few months of the project period demonstrated that the Levy Library's AV collection was deficient in resources suitable for CE and that faculty who came to the library looking for materials for their courses or for individual use found very little in any given area. Strengthening the general AV collection during the next few months stimulated faculty, house staff, and nursing staff use, demonstrated the effectiveness of this type of instructional material, and provided a larger base from which project staff could offer support for CE courses to faculty.

A separate audiovisual center in the library opened in September 1977. Materials that had previously been housed in closed stacks behind the circulation desk, were transferred to open stacks where they were accessible for browsing. Coordination with other library sections was established and procedures were developed for acquisitions, cataloging, circulation, and reference (4).

As access to the AV collection changed, so did its user population. There was an observable increase in the numbers of casual users of noncourse related materials, as the center facilitated access to programs and playback equipment. General use by students, nurses, faculty, and attending physicians increased, and house staff use rose 500% between February and August 1978. This type of use could be considered nonstructured and self-motivated CE.

In August 1977, the Project Librarian began to meet with selected CE faculty to assess their needs and to preview materials prior to purchase. An active promotional program was also initiated at this time. Mediagraphies (bibliographies of AV materials) related to a given course or to a specific subject area were compiled. These mediagraphies are updated regularly and are displayed in the audiovisual center and distributed upon request.

Project staff prepared exhibits and bulletin boards to coincide with CE course offerings and accompanied these displays with course lists that included both print and nonprint materials. During several course sessions, project staff demonstrated related AVs outside the classroom at coffee breaks and lunch hours and encouraged participants to use these items in the library after class. These activities generated interest among others in the Mount Sinai community and stimulated their utilization of the audiovisual center.

Faculty Attitudes

As the project's implementation proceeded, some faculty members contacted were actually less willing to participate in its activities than had been anticipated from responses to the preproposal needs assessment. Although many nursing instructors were eager to incorporate AV programs into their courses, physicians appeared less than enthusiastic. We perceived the importance of identifying faculty attitudes which inhibit participation, and, with the assistance of an educational psychologist, developed an attitude survey instrument to assess faculty attitudes toward their CE students and towards AV in general. We are presently compiling the survey results and anticipate using them to develop new approaches that will encourage additional faculty participation in this project. Evaluations of similar projects in other medical schools have typically assessed faculty and student opinion of specific self-instructional AV materials after those materials have been used. There is little information available on attitudes toward this kind of material before its introduction into an educational program. We anticipate that data generated by our survey can suggest approaches to CE faculty who are currently reluctant to incorporate AVs into their instructional format and can lead to development of a working model for other medical libraries.

Conclusion

Early project results corroborate the importance of and need for promoting the library's role in providing AV and print material support to formal CE programs, as well as to health practitioners engaged in individualized CE; however, they also demonstrate that methods used for undergraduate medical education are not necessarily applicable to CE. In the next eighteen months, project staff will work with the faculty of additional CE courses, including those in health care disciplines outside medicine and nursing, and will modify their approaches as needed to encourage broader participation.

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Simultaneous Presentation of Multiple Myeloma and Acute Leukemia in the Absence of Previous Chemotherapy—Report of a Case

PERUMAL THIAGARAJAN, M.D., M.R.C.P.

It has been known that patients with multiple myeloma who have been treated with alkylating agents have a relatively high incidence of acute leukemia and possibly other neoplasms (1–7). It has been proposed that the chromosome damaging effect of alkylating agents may play a crucial role in the genesis of acute leukemias (1,8). Cytogenic studies have shown that there is a higher incidence of aneuploidy in leukemias complicating the course of multiple myeloma than in leukemias arising de novo (9). This has been attributed to the radiomimetic effect of alkylating agents. However, there have been at least five instances of simultaneous occurrence of acute leukemia and multiple myeloma in patients who have not received any chemotherapy (10–14). Cytogenetic and electron microscopic studies have been done in one case (13). We report yet another case with cytogenetic studies.

Case Report

A 72-year-old black male, seen in January 1978, had a three-month history of increasing fatigue and shortness of breath. He had been suffering from gout for the past seven years and for this reason had been taking allopurinol. In 1973, the patient had transurethral resection of the prostate for benign prostatic hyperplasia. At that time, it was noted that he had a total protein of 9.6 gm, but no further evaluation was done. On present admission, physical examination revealed an elderly, emaciated patient with bilateral axillary adenopathy and hepatomegaly of a 16 cm span. The spleen was not palpable. There were no petechial spots.

Initial laboratory values included a hematocrit of 22% with a hemoglobin of 7.2 gm%, a total white blood count of 41,000/mm^3 and a platelet count of 70,000/mm^3. The peripheral smear showed blast cells with multiple nucleoli and many nucleated red cell precursors. The differential count of the smear was as follows: 12% blasts, 3% promyelocytes, 5% myelocytes, 6% metamyelocytes, 29% polymorphs, 19% lymphocytes, 4% monocytes, and 22% nucleated red cells. The bone marrow aspirate and biopsy showed a hypercellular marrow with marked decrease in the megakaryocytes and other normal cells with diffuse infiltration with blast cells and promyelocytes to 40%. A number of blast cells were peroxidase positive. In several areas of the smears there were immature looking, often multinucleated plasma cells, at times forming a syncytium (Fig. 1a, 1b). Differential count of 1,000 nucleated cells of the marrow was: myeloblasts and promyelocytes 40%, myelocytes 9%, metamyelocytes 3%, bands and neutrophils 4%, erythroid series 13%, lymphocytes 5% and plasma cells 26%. Serum protein electrophoresis showed a monoclonal spike and the immunoquantitation revealed IgA of 1900 mg, IgG of 800 mg and IgM of 40 mg (Fig. 2). Immunoelectrophoresis showed an abnormal precipitin arc for IgA kappa paraprotein (Fig. 3). The urine was negative for proteins and no free light chains were detected in the 24-hour concentrated urine. Chromosome studies done on cultured bone marrow cells showed aneuploidy with an extra C group chromosome (Fig. 4). The metastatic survey showed extensive demineralization in vertebral bodies, pelvis, ribs, the skull and scapula. No "punched-out" lesions were seen.

Over the next few weeks the patient became progressively more anemic and thrombocytopenic and it was decided to treat him with 6-thioguanine and cytosine arabinoside. A partial remission was obtained with persistence in the bone marrow of leukemic cells and abnormal plasma cells. The patient expired five months after the diagnosis, from progressing leukemia.

Discussion

This case offers further evidence that prior chemotherapy is not necessary for the development of acute leukemia in patients with multiple myeloma. The diag-

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From the Department of Hematology, Bronx Veterans Administration Hospital, Bronx, N.Y. 10468.

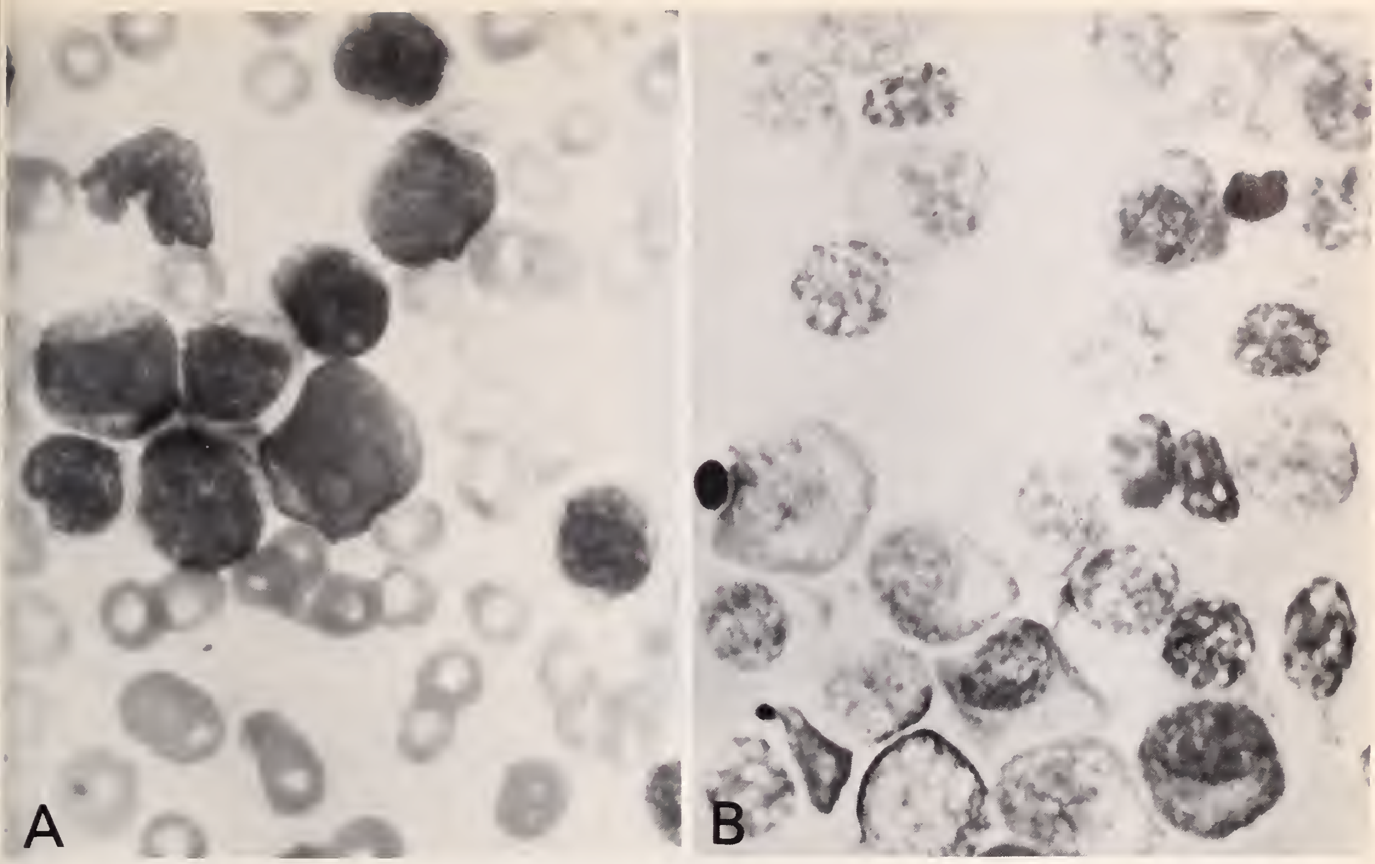

FIG. 1a. Photomicrograph showing blast cells in the marrow.
FIG. 1b. Photomicrograph showing clumps of plasma cells in the same specimen of the marrow.

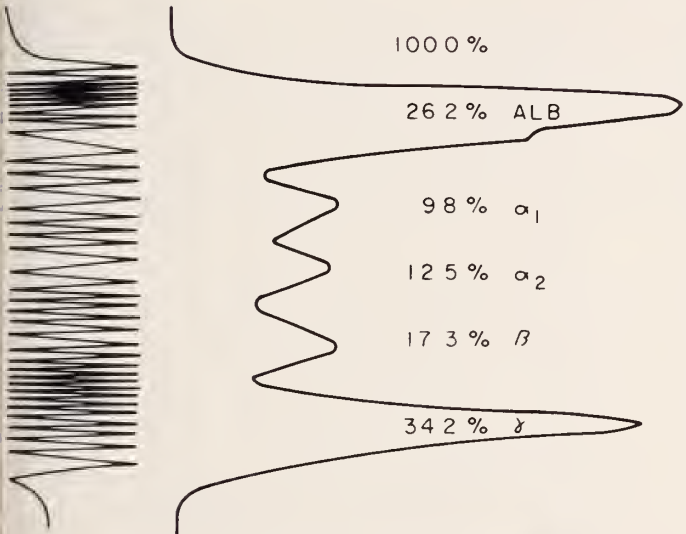

FIG. 2. Protein electrophoresis of the serum.

nosis of leukemia was established by the presence of immature cells in the peripheral blood and infiltration of the bone marrow with peroxidase positive myeloblasts to 40%. The abnormal karyotype with the extra chromosome in the C group had been previously reported in cases of acute leukemia (15).

It is possible that plasma cell proliferation may represent a benign monoclonal reaction described in a number of disorders, including acute leukemias. However, the abnormal morphology of these cells, which constitute more than 25% of the marrow cell population, and the monoclonal IgA of 1900 mg are more characteristic of multiple myeloma than benign monoclonal gammopathy. To our knowledge, only five instances of simultaneous detection of multiple myeloma and acute leukemia have been described in English literature. The authors who initially described this phenomenon proposed several interesting hypotheses to explain this rare combination when there is no identifiable insult to the hemopoietic system such as radiation or chemotherapy. Multiple myeloma per se is associated with a decrease in immuno surveilance and this may have resulted in the failure to remove incipient leukemic clones (13). Osserman proposes that chronic stimulation of the reticuloendothelial system may result in the development of plasmacytic or myelomonocytic dyscrasias and at times these two cell lines may coexist (16). It is interesting to note a similar phenomenon in BALB/c mice which serve as an animal model for multiple myeloma. Intraperitoneal injection of mineral oil in these mice induces plasmacytoma formation. However, acute myelomonocytic leukemia has occasionally been detected after comparable injections intended to produce plasmacytoma (17).

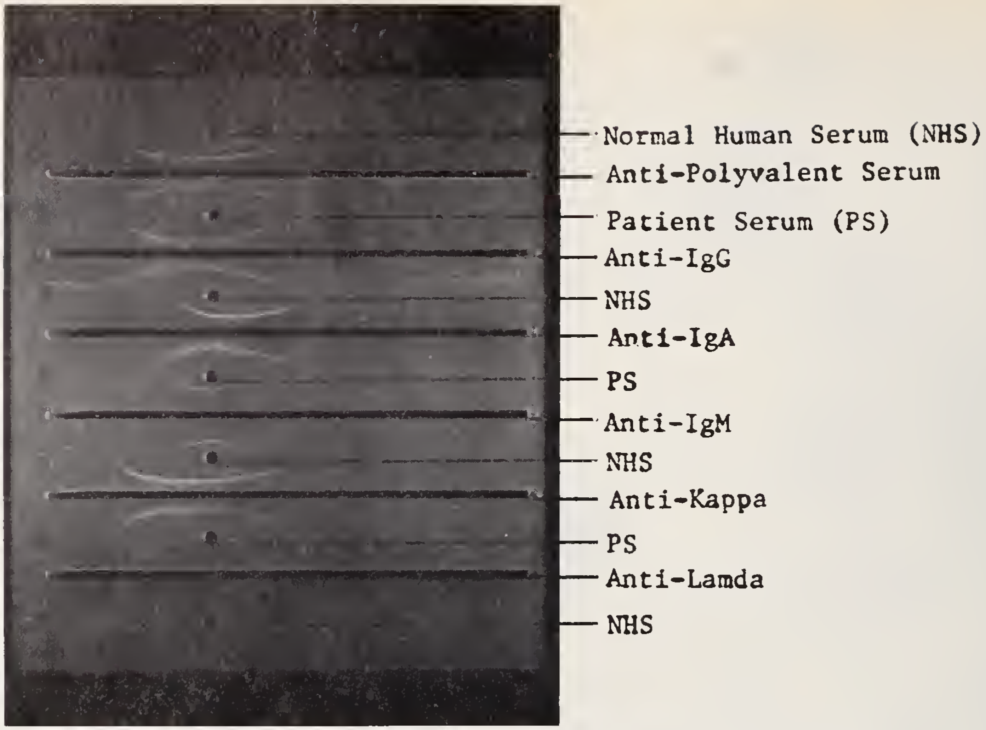
Normal Human Serum (NHS)
Anti-Polyvalent Serum
Patient Serum (PS)
Anti-IgG
NHS
Anti-IgA
PS
Anti-IgM
NHS
Anti-Kappa
PS
Anti-Lamda
NHS

FIG. 3. Immunoelectrophoresis showing the abnormal precipitin arc for IgA kappa.

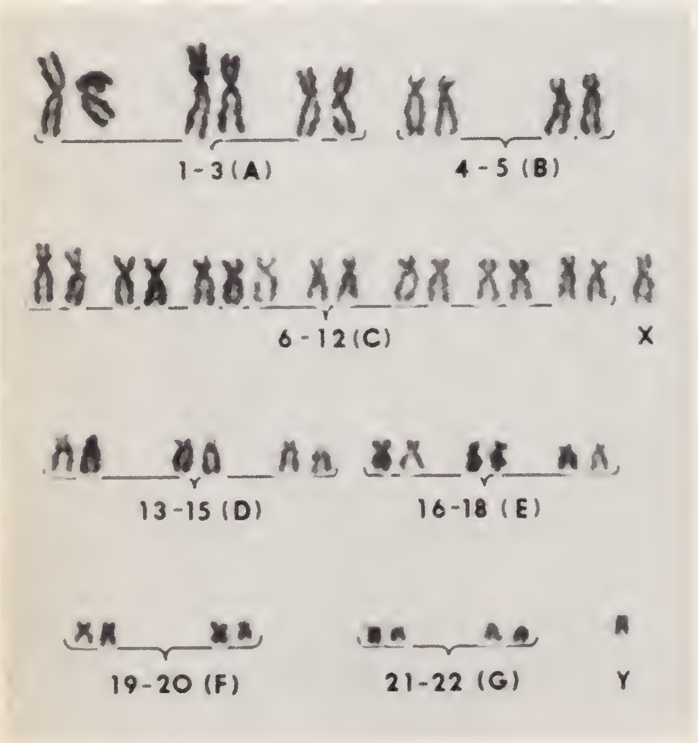
1-3(A)
4-5 (B)
6-12(C)
X
13-15 (D)
16-18 (E)
19-20 (F)
21-22 (G)
Y

FIG. 4. Karotype showing an extra C group chromosome.

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Gallstone Pancreatitis

LEONARD S. BERLINSKI, M.D., RICHARD A. DORAZIO, M.D., F.A.C.S., AND JOHN H. WINKLEY, M.D.

Abstract

Biliary tract surgery was performed on 100 patients with gallstone pancreatitis at the Kaiser Foundation Hospital in Los Angeles during 1967–1977. Sixty-one patients were operated on during the first admission (Early Group) and 39 at a later admission (Delayed Group). In the 61 patients operated on during their first admission, 27 patients (44.2%) had signs of pancreatitis at operation. Of the 39 patients operated on at another admission, ten patients (25.6%) had signs of pancreatitis at operation. The mean elapsed time between admissions in this group was 82.2 days. Cholecystectomy, operative cholangiography, and common duct exploration were performed as indicated. All 100 had gallstones; 51 underwent common duct exploration with 36 having gallstones, gravel or sludge in their common duct. To avoid admissions for recurrent bouts of pancreatitis, the correction of the biliary tract disease should take place during the initial hospital stay (Early Group). There was zero mortality and low morbidity. One patient had a retained common duct stone. There were no cases of recurrent pancreatitis.

Introduction

Since Opie's classic description of the common channel theory in 1901 (1), pancreatitis associated with biliary tract disease has been a much discussed clinical entity.

The etiology of gallstone pancreatitis is still obscure, but the definitive surgical management of the biliary tract disease is undisputed. Controversy does exist, however, about the timing of biliary tract operations following a bout of clinical pancreatitis or hyperamylasemia in patients with cholelithiasis.

Materials and Methods

During 1967–1977, 100 patients with documented gallstone pancreatitis were treated at Kaiser Foundation Hospital, Los Angeles, with a follow-up period ranging from 0.5 to ten years. All patients had x-ray documentation of biliary tract disease preoperatively as well as an elevated serum amylase or urinary diastase on admission.

The records were reviewed for clinical course, length of hospital stay, timing of biliary tract operation, postoperative complications, and recurrence rate.

Patients were divided into an Early Group who were operated on during their first admission, and a Delayed Group, operated on during a subsequent admission. The Early Group consisted of 61 patients, 43 females (70.5%) and 18 males (29.5%), ranging in age from 17 to 80 years old, the mean age being 47.3 years. The Delayed Group consisted of 39 patients, 29 females (74.4%) and ten males (25.6%), ranging in age from 26 to 82 years old, with a mean age of 45.7 years (Table I).

Results

Early Group: The Early Group of 61 patients was treated with nasogastric suction and intravenous fluids until the acute symptoms subsided and the serum amylase level was almost normal; at which time, surgical intervention took place. Seventy-one percent of the patients also received antibiotics. The mean preoperative period was 5.4 days with a range of 1–12 days.

The serum amylase ranged from 400 to 6400 somogyi units (normal 320). The serum bilirubin ranged from 0.2 mg% to 10.6 mg% with a mean of 2.86 mg%. Inspection and palpation of common bile duct was normal in ten patients and no further evaluation was done. Operative cholangiograms were done in 11 patients; they were completely normal. The common bile duct was explored in 40 (65.5%) of the 61 patients; gravel, stones or sludge were found in 30 (75%) (Table II).

In 34 patients a normal pancreas was found at the time of surgery. They had a serum amylase ranging from 440 to 4800 somogyi units, with a mean amylase of 1267 units. In 27 patients, varying degrees of pancreatitis were found, ranging from nodularity to an edematous and enlarged pancreas. In only two cases was a markedly enlarged edematous pancreas found (Table III). The serum amylase ranged from 440 to 6400 somogyi units, with a mean of 2163 somogyi units.

In none of the 61 cases did the condition of the pancreas change the planned procedure, and in none of the

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From the Department of Surgery, Kaiser Foundation Hospital, 1526 N. Edgemont Street, Los Angeles, California 90027.

Requests for reprints should be sent to: Leonard S. Berlinski, M.D., Po Box #93, San Nicholas, ARUBA, Neth. Antilles.

TABLE I

	Total No. of Patients	Female	Male	Age Range (Years)
Early Group	61	43 (70.5%)	18 (29.5%)	17–80 (mean 47.3)
Delayed Group	39	29 (74.4%)	10 (25.6%)	26–82 (mean 45.7)
Total	100	72	28	

TABLE II

Early Group: Common Duct Explorations

Bilirubin Level (mg%)	No. of Patients	No. of Explorations	Positive	Negative
0.2–1.0	19	10	5	5
1.1–2.0	17	10	8	2
2.1–3.0	7	4	3	1
3.1–11.0	18	16	14	2
Total	61	40	30	10

TABLE III

Operative Findings

	No. of Patients	Normal Pancreas	Abnormal Pancreas
Early Group	61	34	27*
Delayed Group	39	29	10

* Only two patients had a markedly enlarged pancreas.

cases was any mention made in the operative notes of difficulties in performing the surgery due to the condition of the pancreas. The mean hospital stay for the Early Group was 14.3 days.

Delayed Group: The Delayed Group of 39 patients was treated with nasogastric suction, intravenous fluids and sedation; these patients were discharged to have their surgery at a later date. The mean time between discharge and readmission was 82.2 days, with a range of 2–288 days.

One patient was readmitted after two days because of severe pain. Seven other patients were readmitted with recurrent bouts of gallstone pancreatitis while awaiting elective surgery. On readmission, their serum amylase ranged from 800 to 4800 somogyi units and they underwent operation on the average of 4.8 days after admission. The remaining 31 patients were admitted electively.

On their first admission, the Delayed Group had a serum bilirubin ranging from 0.2 to 7.1 mg%, with a mean of 2.23 mg%. During their second admission, the common duct was explored in 11 (28.2%) of 39 patients and stones, gravel or sludge were recovered in six (54.5%) (Table IV).

The pancreas was found to be normal at the time of surgery in 29 patients. In ten patients, the pancreas showed evidence of inflammation and nodularity; three of these patients had been readmitted with gallstone pancreatitis (Table III). The other seven patients, however, had not had any clinical indication of ongoing pancreatitis; they had a mean of 67.4 days since their previous bout of pancreatitis. The mean hospital stay for first and subsequent admission for the Delayed Group was 20.1 days.

Complications

There was a zero mortality rate for the entire group of 100 patients. In the Delayed Group postoperative atelectasis occurred in 23 patients 59%. There were two patients with urinary tract infections and one had a wound infection. In the Early Group postoperative atelectasis occurred in 23 patients (59%) and there was one patient with a wound infection. One other patient had a retained common duct stone that was missed on the intraoperative T tube cholangiogram. This patient was treated with Sodium Cholate infusion for four days; the stone had disappeared on a repeat T tube cholangiogram at that time (Table V).

Discussion

Pancreatitis might be caused in some patients by transient obstruction of the ampulla of Vater by migrating gallstones, as shown by Acosta and Ledesma (2). It is possible that the variable time of this obstruction determines the extent of incubation of bile and pancreatic juices, causing activation of enzymes and pancreatitis, as found by Elliott et al in experimental work (3). Perhaps still in others, reflux of duodenal contents into the common bile and pancreatic ducts through a patulous sphincter may be the underlying cause, as suggested by McCutcheon (4). Bartlett (5) offers several cases showing that abnormal muscular activity at the lower end of the common duct and in the adjacent duodenal wall was the underlying cause of gallstones and pancreatitis. Trapnell (6) suggests infection in the common duct and gallbladder as a cause of pancreatitis.

Howard and Ehrlich (7) write that pancreatitis secondary to gallstones is recurrent as long as the patient retains

TABLE IV

Delayed Group: Common Duct Explorations

Bilirubin Level on First Admission (mg%)	No. of Patients	No. of Explorations	Positive	Negative
0.2–1.0	16	3	2	1
1.1–2.0	8	2	2	0
2.1–3.0	6	2	1	1
3.1–8.0	9	4	1	3
Total	39	11	6	5

TABLE V

Complications for the Entire Group of 100 Patients

0	Mortality
0	Postoperative pancreatitis
0	Reoperations
2	Wound infections
1	Retained common duct stone (successfully treated with Cholate)
2	Urinary tract infections

TABLE VI

Mean Hospital Stay

Early Group	14.3 days (5.4 days preop., 8.9 days postop.)
Delayed Group	20.1 days

the gallstones. They found that at least 36% of their patients had recurrent attacks prior to operation. Paloyan et al have shown that a high percentage of patients with gallstone pancreatitis (48.4% in their group) will have recurrent bouts of pancreatitis, forcing readmission prior to their elective surgery (8).

In our Delayed Group, eight patients (20.5%) were readmitted as emergencies while awaiting elective surgery following the first bout of gallstone pancreatitis. They were subsequently operated on without any complications.

Serum amylase levels may be significantly elevated without demonstrable pancreatitis at operation. In our Early Group of 61 patients, for example, 34 patients had amylase values ranging from 440 to 4800 somogyi units shortly before surgery, yet there were no signs of pancreatitis at operation.

Howard and Johnson (9) found common duct stones in 25% of their patients with gallstone pancreatitis. In our total series of 100 patients, 51 (51%) had a common duct exploration and 36 (36%) had stones, gravel or sludge recovered from their common duct.

Surgical correction of biliary tract disease during the first admission in patients with gallstone pancreatitis is recommended by Paloyan et al, Kelly and Elliott (8, 10, 11). Our retrospective review of 100 patients supports this approach. Early operation is not associated with increased mortality or morbidity. The major advantages of early operation are a decrease in hospital stay–in our series from an average of 20.1 days to 14.3 days (5.4 preoperative and 8.9 postoperative)–and an avoidance of recurrent gallstone pancreatitis while awaiting elective surgery (Table VI).

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Aldosterone and Sodium Balance: Towards an Understanding of the Basic Mechanisms

IRWIN M. REICH, M.D., PH.D.*, AND WALTER N. SCOTT, M.D.**

Abstract

The cellular events leading to the stimulation of sodium transport (or reabsorption) by aldosterone (Aldo) are initiated by the nonspecific movement of the steroid across the cell membrane into the cytosol. Here, Aldo binds to a specific protein receptor which undergoes an enzymatic transformation after binding the steroid. This receptor-Aldo complex is apparently responsible for signaling the nucleus to synthesize the messenger RNAs that code for the specific proteins (enzymes) necessary to achieve Aldo's physiologic effect upon sodium balance. Although the precise function of these proteins is not yet known, evidence suggests that they are responsible for 1) enhanced synthesis of adenosine triphosphate (ATP) and/or, 2) specific sodium channels for the permeation of sodium through the plasma membrane of the renal tubular cell.

Introduction

The long-term regulation of sodium balance in humans is mediated primarily by the adrenal corticosteroids. Aldosterone (Aldo), the most important of the mineralocorticoids in humans and most other mammals, has as its primary site of action the distal nephron, where it stimulates Na^+ reabsorption as well as H^+ and K^+ secretion (1). Aldo also affects ion transport in the colon, sweat glands, and salivary glands. Clinically, hypersecretion of Aldo by an autonomous adrenalcorticoid adenoma causes mild systemic hypertension and hypokalemia, while hyposecretion due to adrenal insufficiency leads to volume depletion and hypotension. However, the clinical importance of Aldo is determined primarily by its central role in malignant hypertension, in the edema associated with cirrhosis of the liver, nephrosis and heart failure and, in its evolving role in "essential" hypertension. Therefore, a detailed understanding of the mechanism of action of Aldo should offer opportunities to devise new and more effective modalities for the treatment of these disorders. For instance, it was found that an early event in the mechanism of Aldo's actions on sodium excretion by the kidney is the binding of the hormone to a specific receptor in the tissue (2, 3). This knowledge led to the development of spironolactone (SC-14266), an effective antihypertensive agent that competes with Aldo for the binding site on the receptor in the renal tubular cell. However, despite this advance and the considerable body of knowledge that has been accumulated concerning the mechanism of other types of corticosteroid hormones (4), the cellular events in the stimulation of ion transport by Aldo are not completely resolved. This paper will review our current knowledge of the mechanisms by which these hormones regulate sodium balance and will indicate the direction and promise of ongoing research. The role of Aldo in other orders of vertebrates is reviewed by Bentley and Scott (5).

The Amphibian Urinary Bladder as a Model for the Mammalian Distal Nephron.

The major difficulty in studying the biochemical consequences of aldosterone in the kidney directly derives from the great cellular heterogeneity of the organ. Because only a very small portion of the tissue is responsive to Aldo, most of the assays and measurements necessary to study the effects of the hormone are rendered useless because of the large background arising from the larger mass of unresponsive tissue. Therefore, it would be most desirable to study the hormone using a more or less homogeneous population of responsive cells from the

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From the Departments of Physiology and Biophysics, and Ophthalmology, Mount Sinai School of Medicine of The City University of New York.

* This paper was written during Dr. Reich's final year in the combined M.D./Ph.D. program.

** Dr. Scott is the Molly Berns Senior Investigator of the New York Heart Association.

Requests for reprints should be sent to Dr. Scott, Department of Physiology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, N.Y. 10029.

kidney or similar tissue. In 1958, Bentley showed that exposure of the in vitro urinary bladder of the marine toad, *Bufo marinus*, to antidiuretic hormone (ADH) resulted in an enormous increase in the permeability of the tissue to water, analogous to the postulated effect of ADH upon the distal tubule and collecting duct (6). Leaf, Anderson, and Page (1958) demonstrated that the isolated urinary bladders of *Bufo bufo* and *B. marinus* actively transport sodium from the mucosal (urinary) to the serosal (blood) surface, and that this transport is stimulated by neurohypophyseal antidiuretic hormones, for example, vasopressin (7).

Leaf and his colleagues, after observing that radioisotopes of Na^+ move more rapidly from the mucosa to the serosa than vice versa, concluded that the baseline transport of Na^+ by the bladder is active and that this occurs when the Na^+ concentrations are equal on both sides of the tissue (7, 8). This active transport of Na^+ causes the serosal side to become electropositive by as much as 120 mV under basal conditions. Ussing and Zerahn (1951) had shown that the rate of sodium transport could be measured by the amount of exogenous electrical current required to reduce this spontaneous potential difference across the tissue to zero (9). Leaf determined that this exogenous current, the short-circuit current (SCC), is equal to the net rate of Na^+ transport by the toad bladder under a variety of conditions. By establishing the SCC as a relatively simple means of measuring Na^+ transport in the tissue, the cumbersome and expensive necessity of sodium isotopes for studies of sodium transport was obviated.

Another notable advance was made by Crabbé who demonstrated that Aldo also stimulates sodium transport in the toad bladder (10, 11). Unlike the prompt response observed with ADH, the effect of this hormone upon sodium transport was characterized by a latent period of approximately 1½ hr, and the maximal effect was not observed until approximately 3 hr. The stimulation of Na^+ transport was obtained with physiologic concentrations of hormone (10^{-8} to 10^{-9} M) and persisted for six to eight hours. This work provided the foundation for all the subsequent studies of the mechanism of action of Aldo (2, 12). These experiments thus established the toad's urinary bladder as an inexpensive, readily available research model for the study of the hormone-responsive transport properties of the relatively inaccessible mammalian nephron.

The toad bladder mucosal epithelium consists of a single layer of mucosal cells supported by connective tissue and smooth muscle. These epithelial cells can be classified morphologically into four types, of which the granular (G) cells and mitochondria-rich (MR) cells account for approximately 80% and 15%, respectively (13); the remainder consists of mucus-secreting cells and basal cells. Because the G and MR cells span the epithelium, and are thus in contact with both the urinary fluid and the basement membrane of the tissue, the barrier to the movement of water and solutes through the tissue consists of a single layer of mucosal cells (14). Because each MR cell is apparently in contact with a G cell, Goodman et al suggested cooperative interaction between the two major classes of mucosal cells in the physiologic responses of the tissue (15). Although such considerations of the ultrastructure of the toad bladder might seem unrelated to the mammalian kidney, Stokes, Tisher and Kokko recently demonstrated that the responsiveness of the rabbit collecting tubule to Aldo correlates with the presence in the tubular epithelium of the "dark" cell, which may be analogous to the MR cell of the toad bladder (16). In any event, the toad's urinary bladder, modest in structure and phylogeny, has been a uniquely useful tool for the elucidation of our current understanding of renal function, especially with regard to the hormonal regulation of ion and water balance.

Proposed Mechanisms of Aldosterone-Induced Stimulation of Sodium Transport

The major hypotheses concerning the mode of stimulation of Na^+ transport by aldosterone are based on the premise that exposure of the tissue to Aldo results in the synthesis of new cellular proteins. This idea is an outgrowth of the 90-minute-latent period before the Aldo-induced increase in SCC appears, which suggested to Crabbé (11) that the synthesis of some intermediate (of an unknown nature) is required for the response. It was subsequently found that the Aldo-induced increase in Na^+ transport could be blocked by either puromycin or actinomycin D (2, 17, 18), indicating that RNA and protein constitute the intermediate component(s) postulated by Crabbé. A considerable effort was mounted by several laboratories to isolate and determine the nature of these proteins as a necessary step to defining the mechanism of action of Aldo. Three possible functions for aldosterone-induced protein(s) (AIP) were generally considered (Fig. 1): 1) the AIP may be a component of the plasma membrane of the luminal (urine) surface of the cell, where it acts as a sodium permease, lowering the resistance to Na^+ entry into the cell; 2) the AIP may be the $Na^+ - K^+$ ATPase, or a component of this enzyme, on the serosal (blood) side of the cell, thus increasing the active extrusion of Na^+ from the cell; or, 3) the AIP may be a mitochondrial enzyme(s) that accelerates the formation of ATP fueling the $Na^+ - K^+$ serosal pump, thus indirectly resulting in the increased extrusion of Na^+ from the cell (and across the tissue). It is also quite possible that AIPs are not limited to one of these mechanisms exclusively, but that the effects of the hormone reflect the contribution of AIPs to some combination of these three general mechanisms.

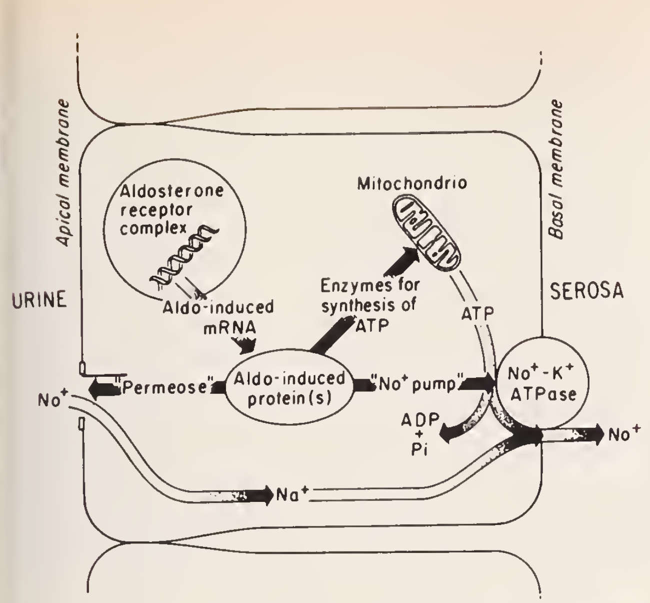

FIG. 1. Proposed mechanisms for the stimulation of sodium transport by Aldo. The Aldo-receptor complex in the nucleus unmasks transcription, and the mRNA codes for Aldo-induced protein(s). These may enhance active sodium extrusion from the cell either directly (Na pump) or indirectly (mitochondrial enzymes leading to increased ATP/ADP), or the protein may act on the apical side as a sodium permease.

These three hypothetical mechanisms can be viewed as offering two fundamental alternatives; that is, either the hormone acts by facilitating the entry of Na$^+$ into the cell from the urinary fluid, or else it acts primarily by enhancing extrusion of Na$^+$ serosally. The first process involves passive ion transfer down an electrochemical gradient, but is assumed to be dependent on the presence of specific low-resistance sites or channels in the luminal plasma membrane. The second process requires active transport since the ion moves against its electrochemical gradient, and the active Na$^+$ pump is evidently located on the baso-lateral portion of the cell membrane. Situated between the luminal entry sites and the serosal Na$^+$ pump is the Na$^+$ transport pool, that portion of the intracellular Na$^+$ that is awaiting transport. It is possible that this pool of Na$^+$, which serves as substrate for the Na$^+$ pump, may also serve to coordinate the mucosal and serosal transporting mechanisms (19). For example, it is possible that an increase in the Na$^+$ pool may stimulate the sodium pump, or that an independent increase in the activity of the Na$^+$ pump may result in an increased permeability of the apical membrane to the entry of Na$^+$ into the cell from the urine side. Thus the mucosal and serosal transport processes may have a complex interrelationship, perhaps of an autoregulatory nature (20).

A number of studies of the intermediate Na$^+$ transport pool have led most researchers to believe that Aldo causes a decrease in the resistance to Na$^+$ influx from the luminal side (21–23). However, rather than review these experiments in detail here, suffice it to say that firm conclusions are difficult to extract from these data. Among the problems in interpretation of Na$^+$ pool measurements is the controversy over whether the observed electrochemical gradient is adequate for the diffusional entry of Na$^+$ across the mucosa; if it is not, it may be necessary to alter the model to include an active Na$^+$ pump in the apical membrane. A second problem is the actual measurement of the Na$^+$ pool; techniques currently available may not be able to distinguish accurately between intracellular Na$^+$ and Na$^+$ immediately distal to the Na$^+$ pump (24, 25). Several of the techniques used to measure the Na$^+$ pool experimentally have been subjected to this criticism (26).

Cellular Events Associated with the Response to Aldosterone

In 1963, Williamson observed that actinomycin D, an inhibitor of the transcription of DNA, blocked the antinatriuretic action of Aldo although the kaliuretic effect was not affected (17). Concurrently, Edelman, Bogoroch and Porter demonstrated that puromycin blocked the Aldo-induced increase in SCC (Na$^+$ transport) across the toad bladder (2). Thus, indirect evidence began to accumulate that the effects of Aldo upon Na$^+$ transport, if not the K$^+$ transport effect, in mammalian kidney and toad bladder were dependent on a series of reactions beginning at the transcriptional level and leading to protein synthesis (27).

Data supporting the evidence for the unmasking of transcription by Aldo was obtained by Castles and Williamson (28, 29) who demonstrated the synthesis of RNA by the rat kidney in response to Aldo. Fimognari, Fanestil, and Edelman (30), also working with rat kidney, found increased synthesis of new proteins in response to the hormone, and also showed that actinomycin D blocks the Aldo-induced antinatriuresis. The latter effect was confirmed in the dog (31).

The picture that emerged suggested that the mechanism of action of Aldo was similar to that which had been proposed for other steroid hormones, for example, estradiol, dihydrotestosterone, and progesterone (Fig. 2). As formulated by O'Malley in 1971, this scheme has steroid hormones enter the target cell by a passive, nonspecific process and then combine with specific receptor proteins in the cytosol (4). After binding, the charged-receptor proteins undergo an enzyme catalyzed transformation in which their physical conformation, as evidenced by their sedimentation coefficient is significantly altered. This transformed, receptor-hormone complex next enters the nucleus where it is bound by acidic proteins of chromatin. Transcription of messenger RNA ensues, leading to the translation of specific cellular proteins, which are the ultimate mediators of the hormone's effects.

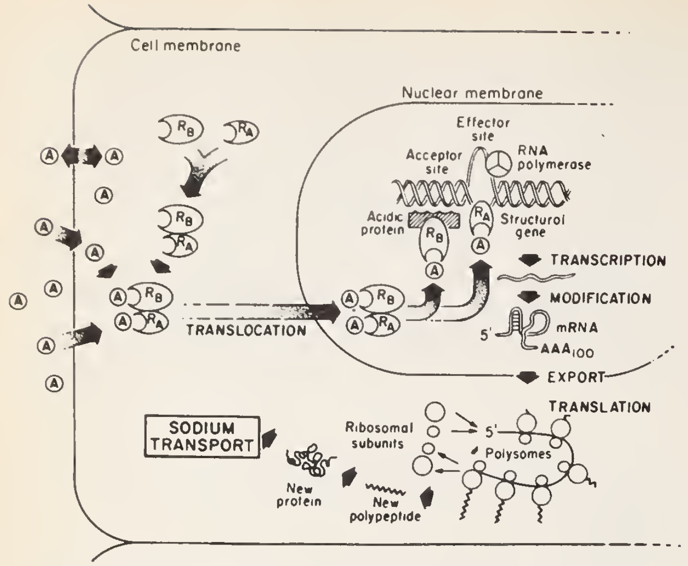

FIG. 2. O'Malley's general scheme for steroid cellular physiology. Steroids permeate the cell membrane and combine with cytosol receptors. The hormone-receptor complex is transformed and migrates to the nucleus where one subunit binds to acidic chromatin and the second subunit binds directly to DNA. Transcription of mRNA follows which is exported to polysomes and translation of effector proteins occurs. In the case of Aldo, the result, by unknown mechanisms, is increased sodium transport.

Tissue Receptors for Aldosterone

Pursuing the nature of the Aldo receptor protein, Edelman and his colleagues showed that a steady-state level of intracellular Aldo was achieved in the toad bladder 30 minutes after exposure to hormone, but that the 90-minute-latent period before a hormone-stimulated increase in short-circuit current (SCC) was consistently noted, regardless of the concentration of hormone used (2). Removal of the hormone bathing the tissue after the initial exposure did not alter either the kinetics or the magnitude of the response. This suggested that an early event of Aldo's action in its target cell is high affinity binding by a specific receptor. Sharp, Komack, and Leaf (1966) found two saturable Aldo-binding sites, one of which was characterized by a high affinity (Kd = 6.7×10^{-11} M), the other by a lower affinity (Kd = 10^{-10} M) (32). However, the high affinity sites were few in number (9×10^{-14}/g tissue) and were saturated at concentrations of Aldo considered to be subphysiological. Both sites were specific, for example, ^{3}H-Aldo was not displaced by inactive steroids, and the steroid with which the greatest degree of displacement was obtained was unlabeled Aldo.

To characterize the Aldo-binding sites in the nuclei of mucosal cells, Ausiello and Sharp (1968) disrupted the nuclei of mucosal cells with detergents and osmotic shock (33). Binding sites numbering 3×10^{-12}/g tissue were found that were 60% saturated at an Aldo concentration of 10^{-7} M. Alberti and Sharp (1969) continued these efforts, isolating three Aldo-binding macromolecular complexes from toad bladder nuclei and showing that bound ^{3}H-Aldo was dissociated from the complexes by pronase, but not by DNAase or RNAase, thus identifying the macromolecular binding sites as proteins (34). One of these complexes had the same number of sites, similar mineralocorticoid specificity, and similar affinity as the lower affinity site described by Sharp, Komack, and Leaf. The remaining two macromolecular complexes were unsaturable and apparently nonspecific. Attempts to isolate the Aldo-binding complex were unsuccessful.

Fanestil and Edelman extended these studies to mammalian kidney, using adrenalectomized rats (35). Following injection of the animals with ^{3}H-Aldo, the kidneys were removed and fractionated into subcellular components. ^{3}H-Aldo was specifically bound in the nucleus, as evidenced by the saturability of the binding in the nucleus and by the ability of 9α-fluorocortisol, another potent mineralocorticoid, to displace Aldo. Nonmineralocorticoid steroids, such as cortisol or estradiol, did not compete for the binding of Aldo. The nuclear receptors, identified as proteins, were half-saturated at an Aldo concentration of 6×10^{-9} M and Scatchard analysis of the data indicated that more than one binding site was involved. Marver et al analyzed the sedimentation properties of this hormone-receptor complex and obtained evidence for transformation of the charged cytoplasmic receptor (36). Both these studies supported the hypothesis that the mechanism of action of Aldo followed the general scheme for steroids proposed by O'Malley (4). Marver et al later showed that the formation of the Aldo-receptor complex in the kidney is competitively inhibited by spironolactones and that the ability of various spironolactones to block Aldo-receptor binding correlated directly with the potency of each compound in blocking the effects of Aldo on the urinary excretion of Na^+ and K^+ (37). Furthermore, the amount of labeled spironolactone bound by the kidneys was quantitatively similar to the binding capacity for labeled Aldo. Recent studies of Aldo receptors isolated from rat kidney indicate that they are distinguishable from the glucocorticoid receptors and that they have a monomeric molecular weight of 67,000 daltons (38).

Sapirstein and Scott (1975), using a technique to separate the two major types of mucosal cells, the MR and G cells, used ^{3}H-Aldo to study the distribution of bound Aldo between the two cell types (39). Intact tissues were exposed to the labeled steroid for a period sufficient for the binding of the hormone and the transformation of the charged receptor, a step that greatly increases the affinity with which the steroid is bound by the protein receptor. It was assumed that this increased affinity of the receptor for Aldo was such that the hormone would remain bound by the mucosal cells as they were removed from the tissue and separated by density gradient separation. It was found that all the displaceable, or specifically bound, ^{3}H-Aldo was localized in the MR cells; the great majority of the hormone was found in the nuclear fraction of this cell. Because the MR cell comprises only 15%–20% of the epithelium, this localization of the apparent site of action of Aldo to the MR was somewhat disconcerting. However, Voûte and his coworkers had previously suggested, on the basis of histochemical studies, that Aldo acted upon the MR cell of amphibian skin (40). This localization of Aldo's effects to a minority population of the mucosal epithelium could account for the previous lack of success in localizing the products of this binding, such as the Aldo-induced RNA and protein. In addition, the identification of one specific cell type as the target for Aldo may have application to the mammalian collecting tubule which contains a morphologically unique cell–the "dark" cell–perhaps having a function similar to that of the MR cell (16).

Aldosterone-Induced Transcription of RNA

In the early studies with aldosterone, it was shown that actinomycin D both blocks the effects of the hormone on Na^+ excretion in adrenalectomized rats (17) and inhibits its effects in the in vitro toad bladder (2). The first direct evidence for Aldo-induced transcription was reported by Edelman, Bogoroch and Porter who demonstrated a modest increase in the incorporation of ^{3}H-uridine into toad bladder RNA before and during the period of increased SCC (2). Significant increases in the labeling of RNA were found biochemically only after 90 minutes, corresponding to the latent period for the Aldo-induced stimulation of SCC (18). However, the interpretation of these results was complicated because the investigators used a concentration of Aldo (10^{-6} M) perhaps sufficient to have a glucocorticoid effect, and by their observation that progesterone also increased RNA synthesis after three hours.

Rousseau and Crabbé subsequently found that the hormone affected an increase in the incorporation of uridine into rapidly labeled RNA, and that most of the rapidly labeled RNA was in the region of heterodisperse nuclear RNA (HnRNA) (41). Increased ^{3}H-uridine incorporation into RNA in response to Aldo was observed even when Na^+ was lacking from the mucosal bath, indicating that the increase in RNA synthesis was not merely a secondary effect of the increased Na^+ transport caused by the hormone (42). Again the value of these experiments was made questionable by the use of "glucocorticoid" concentrations of Aldo (5×10^{-6} M). Nevertheless, the mineralocorticoid specificity of the hormone-induced RNA synthesis was confirmed by Hutchinson and Porter (43) who showed, after incubating tissues in the presence of Aldo and ^{3}H-uridine, that the Aldo-directed increase in labeling of RNA was blocked by spironolactone (500:1). These specific, Aldo-induced spironolactone inhibitable increases in labeled RNA obtained from the nuclear and post-mitochondrial fractions were 10% and 14%, respectively.

Edelman's group extended these studies to the rat kidney, showing increased incorporation of orotic acid (a precursor of uridine) into RNA from kidney homogenates prepared from adrenalectomized rats that had been injected with Aldo (30). Castles and Williamson also found an Aldo-directed increase in the incorporation of labeled uridine into RNA of rat kidney, although the total amount of RNA was also increased (28).

One question that many of these studies did not consider was the possibility that the enhanced incorporation of labeled uridine into RNA was not a direct effect upon RNA synthesis, but was caused by a stimulation of the uptake of labeled uridine by the cells, thereby enriching the specific activity of the intracellular pools of uridine. This problem was specifically addressed by Hutchinson and Porter, who showed that the increase in specific radioactivity of nuclear RNA in epithelial cells scraped from toad bladders after brief treatment with Aldo (7×10^{-7} M) resulted from the incorporation of endogenous, rather than exogenous, precursor (44). Their conclusion was reached on the basis of estimates of the relative contributions of exogenous and endogenous precursor after comparing the rate of incorporation of ^{3}H-uridine into nuclear RNA at two different concentrations of exogenous uridine. The authors supported their conclusion of Aldo-induced accelerated RNA turnover by demonstrating a significant decrease in the concentration of ^{3}H-uridine in the precursor pool of the prelabeled mucosal cells following a chase with unlabeled uridine. Specifically, they found no evidence that Aldo increases the uptake of labeled uridine into the acid-soluble pool. This study was, therefore, particularly noteworthy since it ruled out the possibility that the enhanced incorporation of label into RNA was because of steroid-induced increased cellular uptake of nucleotide. This observation has been confirmed by Yang and Scott using suspensions of disaggregated mucosal cells (unpublished data). However important these studies were, the isolation of the Aldo-induced mRNA had not yet been achieved.

More recent studies have improved on the earlier approaches by using larger amounts of ^{3}H-uridine and by the utilization of affinity chromatography for isolating mRNA. Rossier, Wilce, and Edelman were able to demonstrate a direct correlation between the fractional change in SCC after 180 minutes exposure to Aldo and the fractional change of the specific activity of the cytoplasmic 9–12 S RNA (45). Aldo increased the incorporation of labeled uridine into 9–18 S, nonmethylated RNA, characteristic of mRNA. These data supported the inference that the induction of mRNA synthesis mediates the action of Aldo on Na^+ transport. Scott and Brown confirmed that Aldo-induced labeled RNA exhibits an affinity for poly(dT) and poly(dU), presumably from the presence of poly(dA) in the terminus of the mRNA molecule (46). These investigators subsequently combined this approach with their method of preparatively separating the mitochondria-rich (MR) and the granular (G) cells on Ficoll gradients, and found that the increased labeling of mRNA following Aldo was limited to the MR cells (47). The labeling of RNA peaked at 90 minutes and the labeled RNA was rapidly degraded into smaller fragments. This labeled mRNA was isolated and used as template in a cell-free protein synthesis system to obtain a protein whose molecular weight was indistinguishable from the native Aldo-induced protein (47).

Most recently, studies have been carried out to further assess the roles of poly(A)(+) and poly(A)(−) mRNA in the response to Aldo (48). 3′-Deoxyadenosine inhibited up to 80% of the incorporation of ^{3}H-uridine into poly(A)(+) mRNA of toad bladder mucosal cells, while the drug only partially inhibited the Aldo-induced stimulation of SCC. Actinomycin D had similar effects on ^{3}H-uridine incorporation, but also totally blocked the hormone-stimulated increase in Na^+ transport. The two drugs differed in that 3′-deoxyadenosine, in contrast to actinomycin D, failed to inhibit poly(A)(−) RNA sedimenting between 4 S and 18 S. This RNA species is likely to be poly(A)(−) mRNA (49). The authors, therefore, concluded that an intact poly(A)(−) mRNA pathway is necessary in order to obtain a complete mineralocorticoid effect.

Demonstration and Isolation of Aldosterone-Induced Proteins

The existence of an Aldo-induced mRNA implies the presence of Aldo-induced protein(s) (AIP), and the initial results of Edelman's group, showing a slight increase in the incorporation of labeled amino acids into the total protein of the tissue, supported this hypothesis. But the direct demonstration of the enhanced synthesis of a particular protein was an elusive goal and Edelman's experiments were followed by a number of studies from other laboratories that failed to find evidence for an effect of Aldo upon the biosynthesis of either RNA or protein. The first report of the Aldo-induced incorporation of amino acids into a protein (mol. wt. = 12,000 daltons) of toad bladder mucosal cells did not appear until 1974 (50), but this study was open to criticism on three points: 1) the synthesis of this protein was not induced by dexamethasone, a potent mineralocorticoid in the toad bladder, 2) glucocorticoid concentrations of Aldo (10^{-6} M) were used, and 3) the synthesis of the observed protein may not have been mineralocorticoid-specific, since insulin was as effective as Aldo in increasing the incorporation of amino acids into the putative AIP.

Using a double-isotope protocol, Scott and Sapirstein demonstrated the presence of several AIP's in the toad bladder (51). Hemibladders were incubated in the presence of physiologic concentrations of Aldo (2×10^{-8} M) and ^{35}S-methionine for two hours, while paired control hemibladders were incubated in the presence of ^{3}H-methionine. The two sets of tissues were then mixed, the MR and G cells were removed and separated (52), the cells were sonicated, and the soluble proteins were analyzed by exclusion gel chromatography and isoelectric focusing. Upon analysis of the ^{35}S/^{3}H ratio in each eluted fraction, Aldo-induced proteins having molecular weights ranging from 17,000 to 38,000 daltons were identified exclusively in the MR cells. Glucocorticoids also induced the synthesis of proteins by the mucosal cells, but the apparent molecular weights of these labeled proteins were totally different from those of the AIPs. The authors concluded that the toad bladder MR cell responds to Aldo with the synthesis of several proteins, consistent with their previous finding that this cell was the site of the specific binding of Aldo by the tissue. However, these experiments did not determine the subcellular localization of these induced proteins, an important consideration in defining the protein's mechanism of action.

To address this problem, our laboratory combined the dual-label approach with a technique for the preparation of a tissue fraction enriched in plasma membranes (47, 53). When disaggregated mucosal cells were incubated in the presence of Aldo, AIP's having molecular weights of 170,000, 85,000, and 12,000 daltons (Fig. 3) were identified in plasma membranes prepared from MR cells. Similar results were obtained when intact bladders were incubated with hormone, and the appearance of the newly synthesized plasma membrane proteins was cycloheximide-sensitive (54). When mRNA isolated from Aldo-treated mucosal cells is used as template in a (rabbit reticulocyte) cell-free protein-synthesis system, the synthesis of two steroid-directed proteins is observed and the electrophoretic mobility of one of these proteins is similar to one of the Aldo-induced plasma membrane proteins (mol wt. = 170,000) obtained from the intact tissue (Fig. 4) (47).

Recently, Law and Edelman applied the double-label technique to examine the Aldo-induced synthesis of protein in the rat kidney (55). One hour after adrenalectomized rats were injected with hormone, the animals were killed and nephrectomized, and the renal medullary, cortical and papillary slices were incubated in the presence of either (^{3}H)- or (^{35}S)-methionine for two hours. Following incubation, hormone-exposed and control tissues were combined, and the cells were homogenized and fractionated by differential centrifugation. Polyacrylamide gel electrophoresis (PAGE) of the trichloroacetic acid-precipitable proteins from the medullary cytosol revealed that Aldo significantly increased methionine

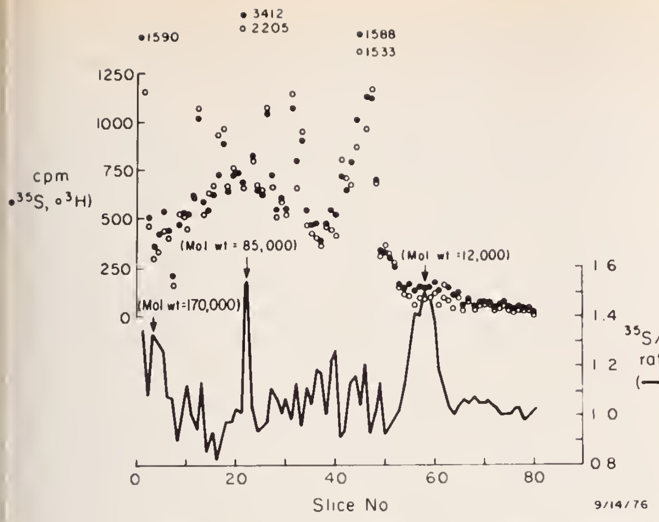

FIG. 3. Aldo-induced proteins in plasma membranes of toad urinary bladder mitochondria-rich (MR) cells. Disaggregated mucosal cells were incubated for 3¾ hours in the presence of aldosterone (7×10^{-8} M) and (^{35}S)-methionine, while cells from paired tissues were incubated in the presence of (^{3}H)-methionine and diluent above. Following incubation, the two sets of cells were combined, mitochondria-rich cells were separated from granular cells on Ficoll gradients, and plasma membranes were prepared from each cell type. These membranes were solubilized and analyzed on polyacrylamide gels, which were sliced, and the ^{35}S/^{3}H ratio was measured in each slice. Shown are the results from MR cells; the increases in the ratio ^{35}S/^{3}H indicate that Aldo stimulated the synthesis of proteins with mol. Wts. = 170,000, 85,000 and 12,000.

incorporation into at least one protein with a molecular weight of approximately 31,000. This effect was inhibited by the pretreatment of the rats with either actinomycin D or spirolactone (SC-26304). These results were consistent with those previously obtained by Scott and Sapirstein in the toad bladder (51).

Using a similar experimental approach, Law and Edelman examined the possibility that mitochondrial citrate synthase (E.C. 4.1.3.7), a key enzyme in the production of ATP, may be synthesized in response to Aldo (56). The enzyme was isolated from kidney tissue either by affinity chromatography and immunoprecipitation with specific antiserum, or by PAGE. Methionine incorporation into renal citrate synthase in response to the hormone was increased by 55% in the immunoprecipitates, and by 43% in the enzyme peak resolved by PAGE. No similar effect was found in response to an equimolar dose of dexamethasone, which has negligible mineralocorticoid activity in the rat, and the response to Aldo was inhibited by either actinomycin D or spirolactone (SC-26304). When the experimental protocol was modified so that labeled methionine was injected in vivo simultaneously with the hormone, Aldo was found to augment methionine incorporation into renal citrate synthase by 55%. Amino acid incorporation into the hepatic enzyme was unchanged. It was not determined if the molecular weight of this induced protein corresponded to that (49,000 daltons) usually ascribed to the subunits of this enzyme (57). The increased synthesis of renal citrate synthase was postulated as reflecting a hormone-controlled modulation of the available ratio of ATP/ADP which could alter both Na^+ conductance and active Na^+ transport (58).

Function of the Aldosterone-Induced Proteins

As it is now evident that Aldo does induce the synthesis of proteins and the isolation of these proteins appears technically feasible, it is perhaps worthwhile to review our current evidence for identifying the physiologic function of these proteins.

1. One approach to demonstrating the presence of a sodium permease utilizes amiloride, an acylguanidine diuretic that inhibits the influx of Na^+ through the apical membrane (59, 60). The toad bladder epithelium binds amiloride reversibly and saturably in a manner that apparently correlates directly with the blockade of Na^+ influx into the cell. Cuthbert and Shum have shown that suppressing endogenous Aldo secretion by immersing toads in saline reduces the number of amiloride binding sites in excised bladders by one-third, whereas the number of binding sites doubles after these tissues are exposed to hormone (61). The steroid effects are abolished by either cycloheximide or actinomycin D, and no similar changes in amiloride binding are observed in response to vasopressin. These data provide strong evidence that an important action of Aldo is to

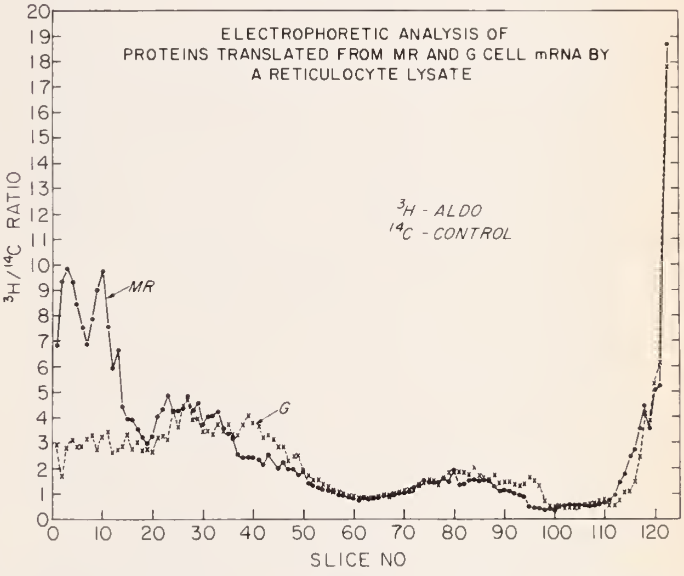

FIG. 4. Analysis of proteins translated from mRNA of Aldo-treated and control MR and G cells. The mRNA was isolated from each of the four sets of cells by affinity chromatography and translated in a reticulocyte lysate system. The Aldo and control samples were incubated in mixtures of ^{3}H- and ^{14}C-labeled amino acids, respectively and after the incubation, the Aldo and Control samples of the MR (and the G) cells were mixed and electrophoresed in a polyacrylamide gel. The gels were sliced and the ^{3}H/^{14}C ratio determined in each fraction.

stimulate sodium influx from the luminal side, although they cannot distinguish whether the AIP is the permease itself, or if it is another membrane component which alters the permease conformation or arrangement in the membrane in such a way that the preexisting permease molecules are simply more accessible to the Na^+ in the urine. Identification of the AIP as Na^+ permease awaits isolation and purification of the AIP, and determining whether it has a high affinity for amiloride or whether its insertion into an artificial membrane results in a Na^+-specific augmentation of ion permeation.

2. While it may be attractive to ascribe a role for an AIP as a $Na^+ - K^+$ ATPase component, attempts at demonstrating such an effect have been unsuccessful. Aldo (10^{-7} M) causes a 35% increase in oxygen consumption in the toad bladder, but no correlative increase in the amount of $Na^+ - K^+$ ATPase activity in tissue homogenates (62). Hill, Cortas, and Walser used a more sensitive ATPase assay to determine whether Aldo produces a change in the kinetic characteristics of this enzyme, rather than in the total amount of activity (63). These investigators examined a variety of conditions, including pretreatment of the toads with either water or saline, or overnight incubation of the bladders in saline, and measured the subsequent response to Aldo. No significant changes in either the total amount of $Na^+ - K^+$ ATPase or in the kinetics of the reaction were observed under any set of conditions. When the enzyme activities at low Na^+ concentrations in the control and hormone-treated tissues were compared by Hill plot analysis, they were found to be identical. Although it remains possible that the enzyme activity in the intact epithelium may not correlate well with that in tissue homogenates, these data constitute indirect evidence that the induction of an $Na^+ - K^+$ ATPase component is not a significant mediating event in the action of Aldo. More direct evidence that the $Na^+ - K^+$ ATPase is not an AIP may be drawn from the recent experiments in our laboratory (47). The molecular weights (170,000, 85,000, and 12,000 daltons) of none of the AIPs identified in the membranes of Aldo-treated mucosal cells correspond to the molecular weights recently reported for the subunits of the $Na^+ - K^+$ ATPase (116,000, 62,000, and 26,000 daltons) isolated from the toad kidney (64).
3. Direct evidence that Aldo may induce the synthesis of an enzyme of the tricarboxylic acid (TCA) cycle has been obtained recently (56), and has been reviewed in a previous section. The basis for these experiments was the observation by Kirsten et al that Aldo (10^{-7} M) increased the citrate synthase activity in the toad bladder by 25% two hours after treatment, and that the enzyme activities of isocitrate dehydrogenase, glutamate dehydrogenase, glutamate-oxaloacetyl transaminase, and malate dehydrogenase were also increased (65). Indirect support for this concept of Aldo-mediated stimulation of the TCA cycle was obtained by Kirchberger et al, who used the rate of generation of $^{14}CO_2$ from glucose labeled at either C-1 or C-6 to show that Aldo decreased the activity of the pentose shunt pathway in the toad bladder while simultaneously increasing the oxidation of glucose by the TCA cycle (66).
4. The toad urinary bladder (both in vivo and in vitro) can respond to Aldo with an increase in the rate of acidification of the urine (67). The acidification function is generally related to carbonic anhydrase activity in the tissue, as significant amounts of this enzyme have been found in the toad bladder epithelium and the process is inhibited by acetazolamide (52). Because this response of the toad bladder to Aldo is blocked by cycloheximide, the implication is that Aldo may stimulate the synthesis of carbonic anhydrase (67). Aldo's stimulation of acidification could either be independent of the hormone's stimulation of SCC, or, as proposed by Voûte, Hanni, and Amman (40), be related indirectly, such as, acidification of the microenvironment of the luminal aspect of the membrane could moderate the permeability of the membrane to Na^+. However, purification and analysis of carbonic anhydrase from toad bladder mucosal cells following double-label amino acid incorporation experiments failed to reveal any increase in the labeling of carbonic anhydrase as a result of exposure to Aldo (7×10^{-8} M) (54).
5. Both the Na^+ transport response (68) and the hydro-osmotic response to vasopressin (69) are reported to be augmented by Aldo in this tissue. Studies of the hydro-osmotic effect also showed that an increased response is noted when Aldo-treated bladders are exposed to exogenous cyclic AMP (cAMP), suggesting a common mediating step distal to the stimulation of adenylate cyclase. Because adrenalectomized animals manifested abnormalities in the excretion of salt and water, and particularly in the function of the distal nephron (70, 71), the data seemed to be related to renal function in adrenal insufficiency. However, more recent data casts some doubt on the synergistic role suggested for Aldo and vasopressin in the toad bladder with respect to Na^+ transport. The SCC response of the steroid-treated tissues was the same as the controls when the data were expressed as a percentage increase over baseline values after the addition of peptide (72). In fact, when the original data of Fanestil, Porter, and Edelman (68) are analyzed in

this manner, their conclusion that Aldo augments the ADH-induced increase in Na^+ transport is not supported. These authors also determined that the in vitro hydro-osmotic synergism between Aldo and neurohypophyseal hormones is only observed at low concentrations of peptide (1 mu/ml) which have a submaximal effect. More recent studies have reported that the kidney of the mineralocorticoid-deficient dog exhibits normal concentrating and diluting capacities (73), casting doubt on the relevance of the original toad bladder studies to renal function.

6. Liu and Greengard have investigated the effects of Aldo on phosphatase activity in the toad bladder and found it to be increased (74). Since this response was inhibited by actinomycin D and cycloheximide (as well as by spironolactone), they hypothesized that Aldo induces the synthesis of a phosphatase which acts with cAMP to control the degree of phosphorylation of a unique protein, protein D, and thereby regulate the rate of Na^+ transport. Other data, however, showing that vasopressin similarly decreases membrane protein phosphorylation (75), suggests that the dephosphorylated protein is involved in the regulation of the hormonally controlled hydro-osmotic flux rather than the natriferic response.
7. Goodman et al proposed that a fundamental mechanism of action of Aldo may be to alter the fatty acid metabolism of membrane phospholipids (76). It was subsequently demonstrated that Aldo specifically enhances both the elongation and desaturation of oleic acid and the recycling of ^{14}C-acetyl-CoA derived from ^{14}C-oleic acid into membrane phospholipid fatty acids in toad bladder exposed to hormone for four hours (77). Extending these studies, Lein et al showed that TPIA, an inhibitor of acetyl-CoA carboxylase, blocked Aldo's stimulation of Na^+ transport in the toad bladder and inhibited both the hormone-induced stimulation of lipid synthesis and the increase in weight percentage of phospholipid long-chain polyunsaturated fatty acids (78). TPIA itself, which does not inhibit basal Na^+ transport, had no effect on protein or RNA synthesis. Scott, Reich and Goodman demonstrated that TPIA inhibits the incorporation of specific Aldo-induced proteins into the mucosal cell plasma membranes (79). The electrophoretic mobility of these proteins is apparently identical to that of the Aldo-induced proteins in the plasma membrane previously described by Scott et al (47). Although it is possible that TPIA directly and selectively inhibits the synthesis of these proteins, it would appear more likely that the inhibitor blocks the synthesis of lipids necessary for the incorporation of the Aldo-induced protein into the matrix of the membrane.

Phospholipase A2 has been shown to shorten the latent period that is characteristic of the stimulation of SCC by Aldo (76) and phospholipase C simulates the effects of Aldo upon Na^+ transport in the frog skin (80). These observations suggest that the Aldo-induced proteins may be enzymes involved in regulating the composition and turnover of these phospholipids and provide further evidence that Na^+ transport in epithelial tissues is dependent on the fatty acid composition of membrane phospholipids. This function of the AIP(s) may or may not be exclusive of a direct role of hormone-induced proteins acting directly in the membrane transport process.

Conclusions

The precise mechanisms by which Aldo modulates the reabsorption of sodium by the mammalian nephron are not yet determined. However, it seems apparent that the biochemical and thus, the physiologic events include the synthesis of specific messenger RNA's by a specific population of cells in the target epithelium. The mRNA's, in turn, code for the synthesis of several proteins, some destined for the plasma membrane, others for the cytosal. The purification and characterization of these proteins appear within our grasp and this information may resolve the controversy over the basic mechanism of sodium transport through the renal tubular epithelium.

Acknowledgements

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Hilar Enlargement Twenty Years Following Resection of a Renal Cell Tumor

LEE B. BERMAN, M.D., ANDREA-C. V. GIARDINA, M.D., AND DOROTHY ESTES, M.D.*

Abstract

A 69-year-old man was admitted with asymptomatic enlargement of the right hilum 18 years after resection of a papillary cystadenocarcinoma of the kidney. He has remained asymptomatic two years following discovery of the mass which, histologically, resembled the original tumor. This case demonstrates the longest interval between the discovery of renal cell carcinoma and hilar metastasis in the literature. We emphasize that renal cell tumors may metastasize to the hilum late, behave as a low grade malignancy in the hilum, and should be considered in the differential diagnosis of asymptomatic hilar enlargement.

Renal tumor metastasis to the hilum has been described as a rare cause of hilar adenopathy (1, 3, 5). These patients generally have had other manifestations of metastatic disease at the time they had hilar nodal enlargement (3, 5) and in no case did hilar adenopathy occur later than three and a half years following the discovery of the primary tumor. We describe an asymptomatic patient with a solitary metastasis of a renal cell carcinoma to the hilum twenty years after resection of the primary tumor.

Case Report

The patient, a 69-year-old man, was admitted to Presbyterian Hospital in September 1957 with hematuria. Cystoscopy revealed cystitis cystica and glandularis. He was readmitted four months later with recurrent hematuria, left flank pain, and left flank mass. A ten cm tumor in the lower pole of the left kidney was found and a nephrectomy performed. Grossly the tumor was described as soft, orange, and necrotic with areas of hemorrhage. It was entirely encapsulated except in the area where surgical biopsy had allowed escape of tumor contents into the kidney. Histologically, the tumor was described as papillary cystadenocarcinoma (Fig. 1). The patient received 4500 rads to the left flank and was subsequently followed in the medical clinic for adult onset diabetes and hypertension. Serial chest x-rays through January 1973 were normal. In September 1976, a prominent right hilum was noted that was anterior and lobulated. However, a retrospective review of chest x-rays revealed that the right hilum was definitely enlarged in April 1976 and probably enlarged in April 1975. He was admitted in October 1976 for a work-up that included bronchoscopy, mediastinoscopy and liver-spleen scan, all of which failed to identify the tumor. Intravenous pyelogram and cystoscopy revealed chronic cystitis but no tumor. The patient declined thoracotomy. In March 1978, the chest x-ray showed further enlargement of the right hilum (Fig. 3) and the patient agreed to thoracotomy. At operation in May 1978, the patient had an unresectable hilar mass. Histologically the tumor was identical to the original renal neoplasm (Fig. 2). Metastatic work-up included normal liver function tests, and a liver scan that was equivocal for an isolated metastasis. He was discharged to receive radiotherapy to the right hilum.

Discussion

Arkless first described mediastinal metastasis of renal cell carcinoma in 11 of 152 patients or seven percent of cases reviewed but did not specify whether these were hilar, carcinal or paratracheal nodes (1). This high percentage of renal tumor metastatic to the hilum was confirmed by Lang, who found nine of 112 cases or eight percent of renal tumors with hilar metastasis (4).

In most of the reported cases of renal tumor metastatic to the hilum, both the primary tumor and metastasis were discovered at the same time (3, 5, 6, 8). There was an interval between the discovery of the primary tumor

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* From the Department of Medicine, Columbia Presbyterian Medical Center, New York, N. Y., and the Departments of Medicine and Pediatrics, Mount Sinai School of Medicine, CUNY, New York, N. Y.
Reprint requests should be sent to Dr. Lee B. Berman, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, N.Y. 10029.

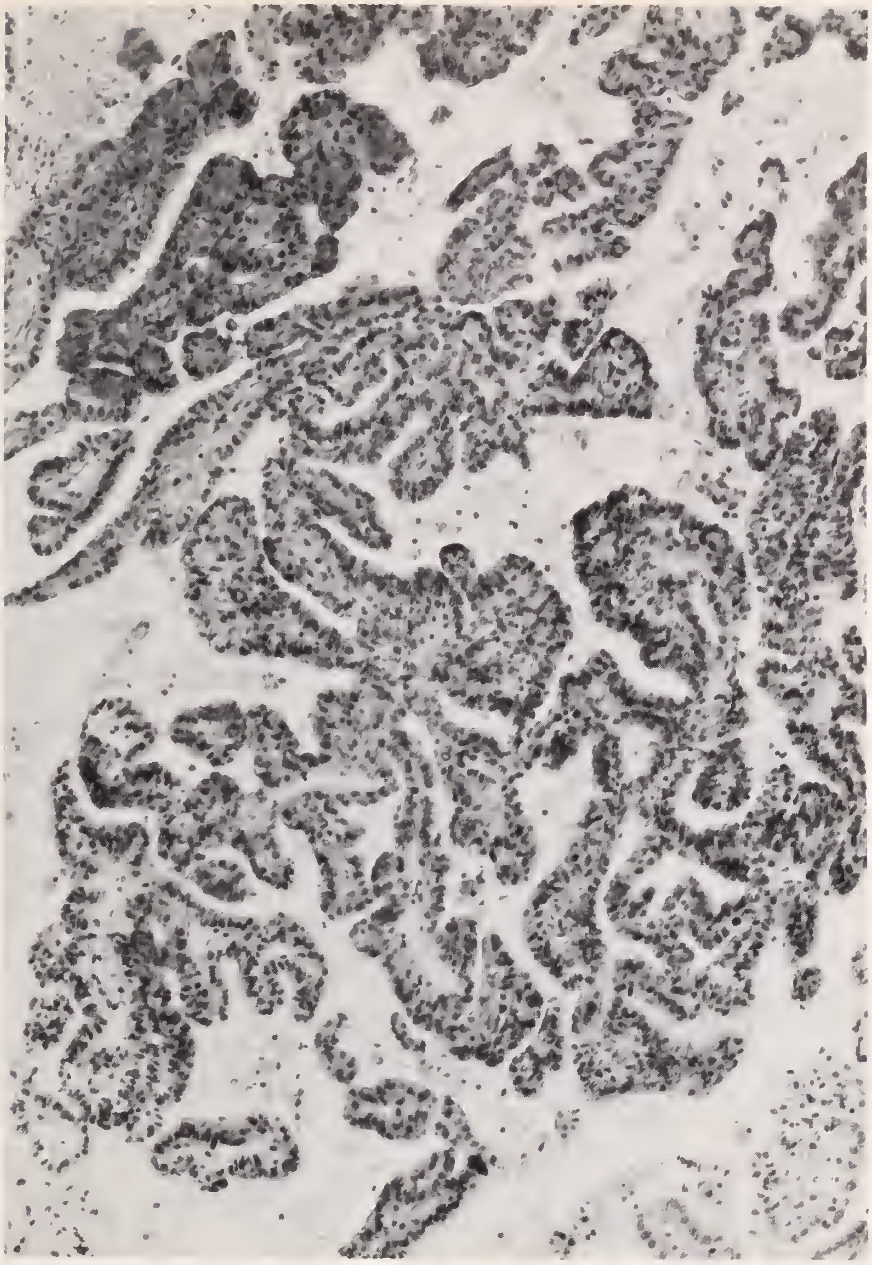

FIG. 1. Biopsy of the original renal tumor (1958), that shows papillary cystadenocarcinoma (H & E, × 100).

and the radiologic appearance of hilar enlargement in four cases in the literature (5, 8), the longest being 3½ years (5).

Reports vary as to prognosis in patients with renal tumor metastatic to the hilum. In Lang's series, patients survived from three weeks to six months with a mean of 1.4 months from the diagnosis of mediastinal metastasis. This compared to an average of 11 months survival in patients with renal tumor metastatic to other parts of the thorax. Lang concluded that dissemination to the hilar nodes represented a more aggressive form, or a more advanced stage of renal cell carcinoma. Others have reported longer survival (3, 5, 8), the longest being three years in a patient reported by Wright (8).

It is difficult to determine from a review of the literature what percentage of patients with hilar nodal enlargement represent renal tumor metastasis. However, in an asymptomatic patient with normal physical examination and bilateral hilar nodal enlargement, metastasis from an extrathoracic tumor is rare (7). It is also difficult to determine what percentage of patients with renal tumor metastic to the hilum also had metastasis elsewhere. Of the few cases described in detail, most had additional metastasis to either the pulmonary parenchyma or other nodal tissue (5, 6, 8).

Renal cell adenocarcinomas have been described as having alveolar, papillary and tubular patterns, with both clear and granular cell varieties. Many tumors have

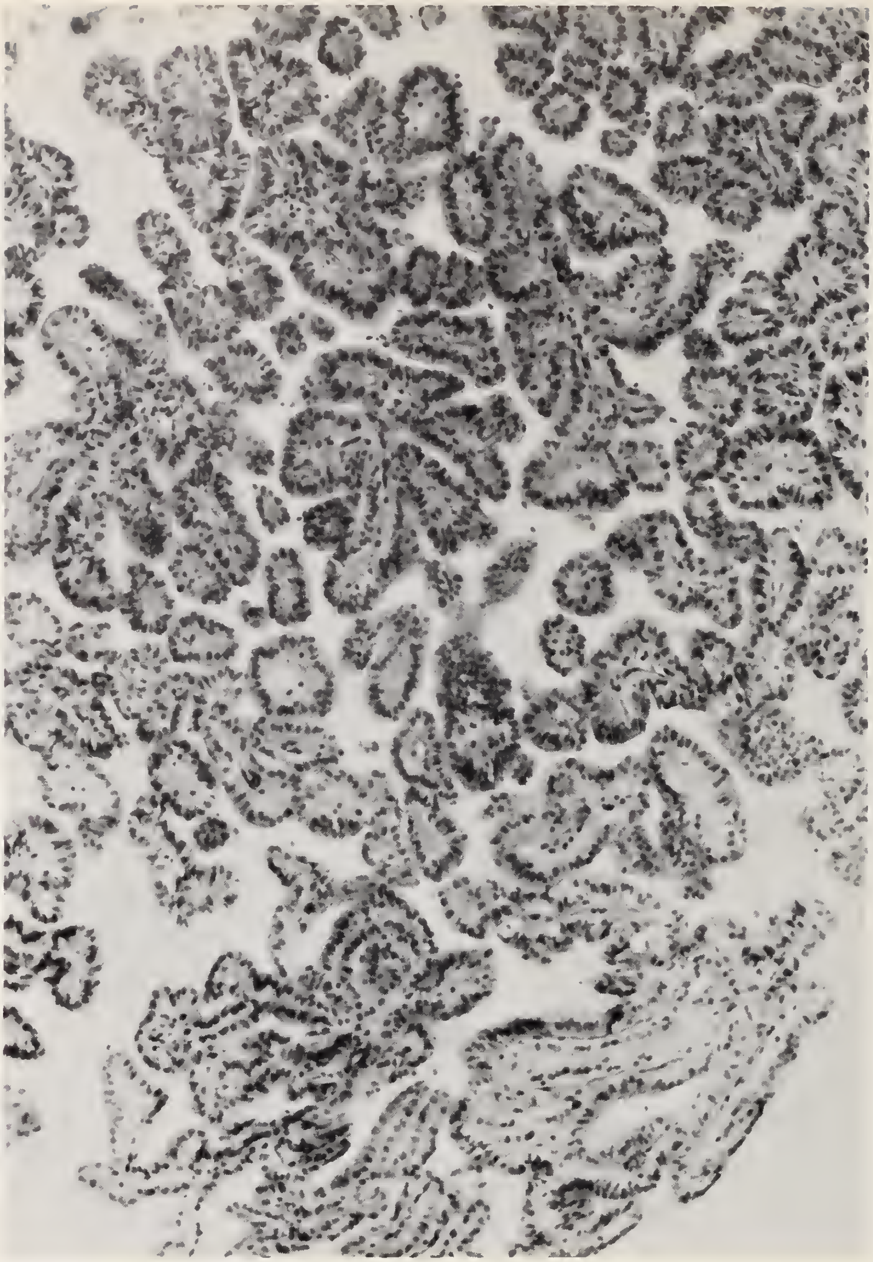

FIG. 2. Biopsy of the right hilar mass (1978). Papillary cystadenocarcinoma similar to the original tumor is seen (H & E, × 100).

features of more than one histologic type and it is unclear if renal cell tumor histology is clinically significant (2). The specific histologic pattern of renal cell carcinoma that metastasizes to the hilum was not commented upon in most reports (1, 3, 4, 6, 8). However, all three cases described by Reinke, in which the histology was specified, were papillary adenocarcinoma (5).

The mode of spread of renal tumors to the mediastinum is uncertain. In Wright's series, all 11 patients had metastasis to the right hilum and only two had bilateral hilar enlargement. He postulated that tumor spread was directly to the right hilum via lymphatics in the inferior pulmonary ligament and proposed that the right hilum is "virtually a regional lymph node of the kidney" (8). Others (4, 5) have regarded hilar metastasis as the result of lymphatic dissemination with retrograde flow from the thoracic duct into bronchomediastinal and peribronchial lymphatics, possibly due to incompetence of lymphatic valves. Seaman speculated that tumor emboli to the pulmonary arteries may enter the peribronchial lymphatics that drain anterograde to the hilar nodes (6).

Our case is exceptional in that hilar metastasis appeared 18 years after discovery of the primary tumor and remained asymptomatic during at least 25 months and probably 37 months following detection. We conclude that renal cell carcinoma may metastasize to the hilum

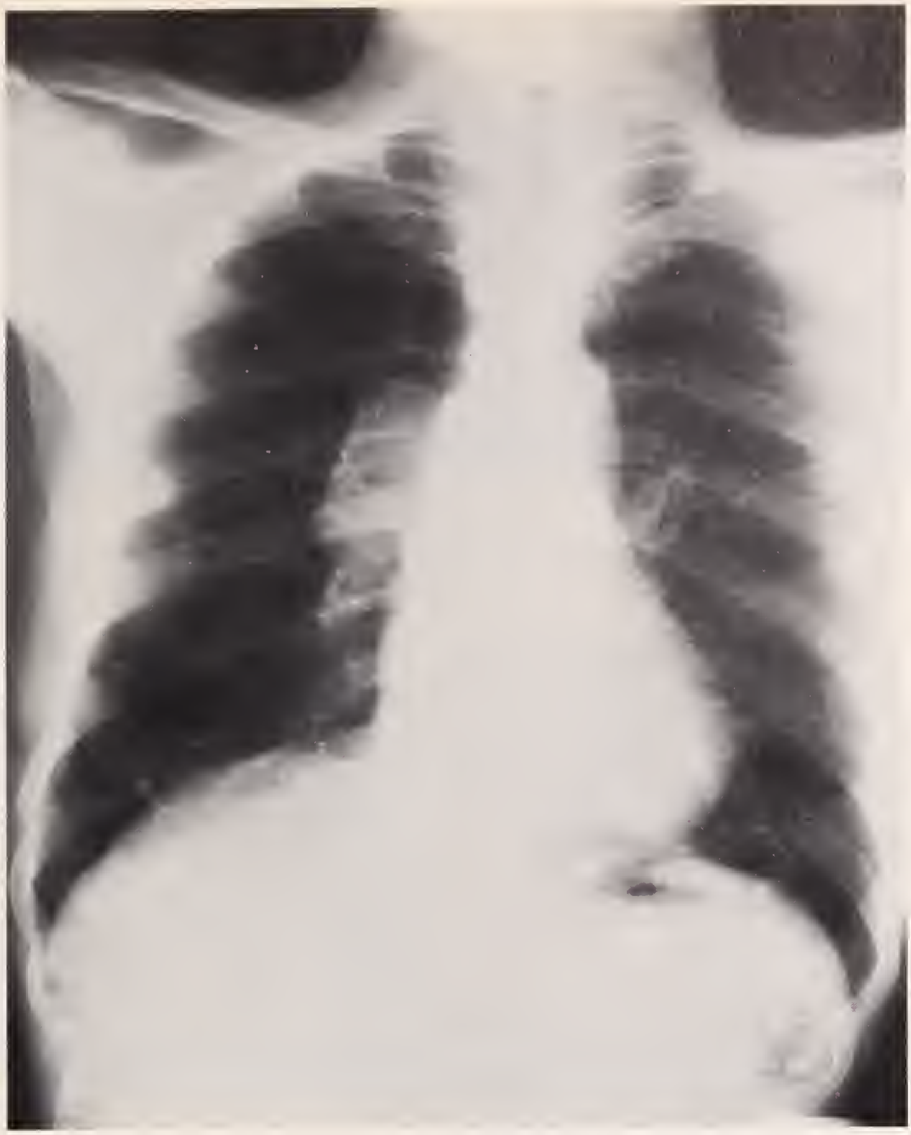

FIG. 3. Chest x-ray PA in March 1978. There is a prominence of the right hilum, which is anterior and lobulated.

late, behave as a low grade malignancy in the hilum, and should be considered in the differential diagnosis of asymptomatic hilar enlargement.

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Villous Adenoma with Severe Fluid and Electrolyte Depletion: Report of a Case

TOMAS HEIMANN, M.D., CHANGYUL OH, M.D., AND ARTHUR H. AUFSES, JR., M.D.

Abstract

This is a case report of a 74-year-old woman who had a rectal villous adenoma associated with severe fluid and electrolyte depletion. This condition is usually found in elderly patients and prompt excision is necessary to eliminate the source of fluid and electrolyte loss. In this instance, it was successfully managed with wide, local excision using a posterior proctotomy, preserving full fecal continence.

Severe fluid and electrolyte loss associated with rectal villous adenoma was first described by McKittrick and Wheelock in 1954 (1). This condition, however, remains a rare entity. Only scattered case reports have been published and several recent large series of patients with villous adenoma do not include any cases with this problem (2–10).

Case Report

A 74-year-old female was transferred from another institution with a history of severe diarrhea and rectal incontinence, associated with mental disorientation and weight loss. Physical examination on initial admission revealed an elderly disoriented female with severe dehydration. On rectal examination, there was a soft pedunculated mass. The serum electrolytes showed a sodium of 115 mEq/l, chloride 59 mEq/l, potassium 1.8 mEq/l, CO_2 content 15 mEq/l, BUN 250 mgm/100 ml and the serum albumin was 2.4 gm/100 ml. She was treated with intravenous fluids with return of the electrolytes and BUN to normal. Sigmoidoscopy revealed a soft mass approximately 8 cm by 11 cm, which was partially prolapsed and occupied half the rectal circumference. It was located anteriorly and in the right lateral rectal wall, starting at 6 cm from the anal verge and extending to 17 cm above. Multiple biopsies showed villous adenoma without malignant changes.

After correction of the electrolyte abnormalities, the patient underwent submucosal excision of the villous adenoma using a posterior proctotomy. The lesion was exposed by incising the posterior wall of the rectum and uppermost part of the external sphincter, including the puborectalis muscle. During the dissection, two areas were encountered where the tumor was adherent to the circular muscularis. In these two places a portion of the deep muscular layer was removed with the rest of the specimen (Fig. 1). The postoperative course was uneventful except for delayed wound healing and temporary urinary retention. Microscopic examination of the lesion revealed a villous adenoma with two small areas of carcinomatous change invading the submucosa. Two years following surgery the patient remains well, she is fully continent and there is no evidence of recurrence.

Discussion

The surgical management of these cases is extremely difficult because of the anatomical location and ambiguous nature of the tumor. Most of them are found in poor risk patients and prompt removal of the tumor is necessary to eliminate the source of fluid and electrolyte depletion. When there is no evidence of malignancy, these large lesions can be removed by a variety of procedures that preserve continence (11–14). Local excision appears to be adequate even when noninvasive carcinoma is present (11, 13). Abdominoperineal resection is the procedure of choice in patients with invasive malignant tumor. Frequently, however, preoperative biopsies are reported as benign and an area of malignant degeneration is only discovered after the entire lesion is removed (15). Although in this case two minute areas of carcinoma infiltrating the submucosa were present, it was elected not to do an abdominoperineal resection due to the patient's advanced age and poor physical condi-

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From the Department of Surgery, The Mount Sinai School of Medicine of The City University of New York, New York, N.Y. 10029.

Requests for reprints should be sent to Tomas Heimann, M.D., Department of Surgery, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, N. Y. 10029.

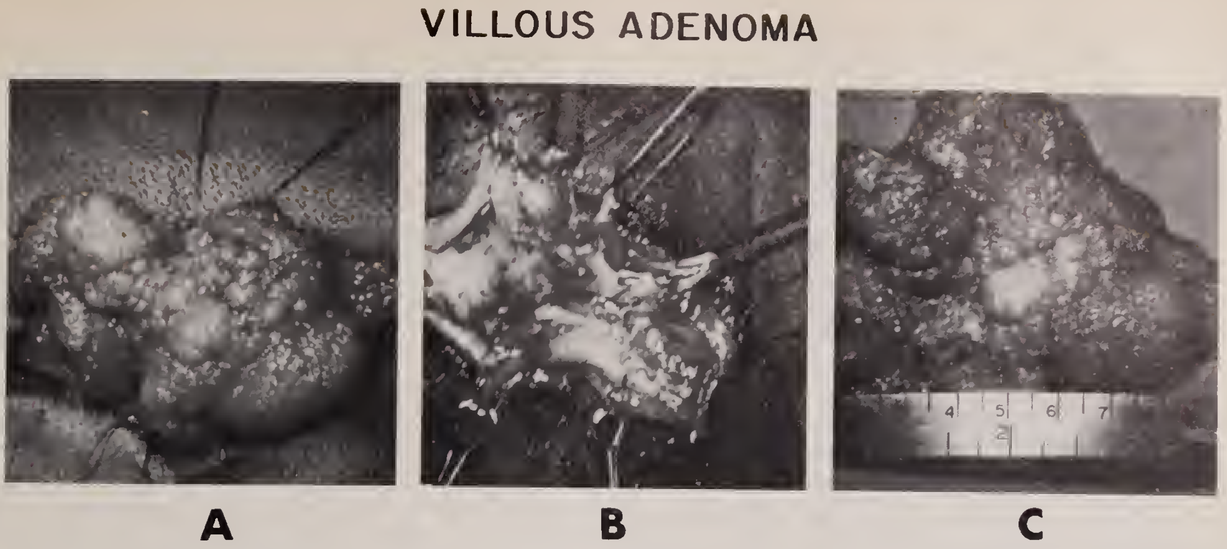

FIG. 1:. "A" shows the lesion prior to excision as exposed by the posterior proctotomy. In "B" the rectal muscular layer is seen after the villous adenoma was completely excised. "C" shows the specimen.

tion. Finding fixation of the lesion to the submucosa in the process of dissection is indicative of invasion. In selected cases, these areas may be completely excised by removing full thickness of the bowel wall en bloc with the remainder of the specimen. This patient has remained well for over two years with no evidence of recurrence.

The management of patients with villous adenoma must be individualized. This is especially true in the elderly poor risk patient with large, fluid-losing rectal villous adenoma. These tumors are of low grade malignancy and, occasionally, local resection with preservation of continence may be the procedure of choice even in the presence of microscopic islands of submucosal infiltration.

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Sodium Nitroprusside and the Pressor Response to Laryngoscopy and Intubation

GARRY S. SKLAR, M.D.* AND YASU OKA, M.D.**

Laryngoscopy and endotracheal intubation have long been recognized as stimuli leading, in some instances, to a severe hypertensive response. This response described in 1951 by King and associates (1), consists of hypertension, tachycardia and arrhythmias, and its severity is unpredictable. It usually is transitory and of no great significance, but hypertensive patients may have serious consequences. A recently published report by Fox et al emphasized these complications (2). They reported that poorly controlled hypertensive patients may be prone to congestive heart failure and rupture of cerebral aneurysms. We have utilized sodium nitroprusside acutely to lower blood pressure before inducing anesthesia and wish to report our technique.

Materials and Methods

Seven adult patients scheduled for emergency surgery were noted to be severely hypertensive preoperatively. Blood pressures measured with a standard blood pressure cuff were noted on the patient's chart. The urgency of surgery precluded delay until medical treatment could control the blood pressure. Therefore, it was decided to lower acutely the patient's blood pressure before induction of general anesthesia.

Fifty ml of a solution of sodium nitroprusside in a concentration of 0.01% was placed in a Harvard infusion pump with tubing leading "piggy-back" to the patient's intravenous infusion. In the operating room, the patient's electrocardiogram was monitored continuously and blood pressure was monitored every 10 seconds by means of a standard Riva-Rocci cuff. A target diastolic blood pressure of 90 torr was arbitrarily established as safe for induction of general endotracheal anesthesia, and sodium nitroprusside was infused until this pressure or lower was reached. Simultaneously, oxygen 5 1/min was administered by means of a tightly fitting face mask. At this point, the sodium nitroprusside infusion was discontinued and general anesthesia was immediately induced. Thiopental sodium was administered intravenously until there was a loss of the lid reflex followed immediately by a paralyzing dose of succinylcholine. The patients were in a 15° head-up position and cricoid pressure was applied. Laryngoscopy and endotracheal intubation were swiftly performed, the cuff inflated, and general anesthesia with nitrous oxide and oxygen or nitrous oxide, oxygen and halothane was commenced. Throughout the induction, blood pressure was monitored every ten seconds. In all cases, elapsed time from discontinuation of sodium nitroprusside to completion of endotracheal intubation was less than 2½ minutes.

Results

The sodium nitroprusside infusion in all cases acutely lowered the blood pressure (Table I). The target diastolic blood pressure was overshot as the blood pressure continued to decline after discontinuation of sodium nitroprusside or following injection of thiopental. The lowest level is recorded in Table I. The acute lowering of blood pressure was accomplished with all patients awake and they all stated that they felt warm but otherwise had no complaint. The lowered blood pressure following induction was immediately reversed by the laryngoscopy and intubation. In all cases, blood pressure rose in response to laryngoscopy and intubation and, in three of the seven patients, there was a rise of diastolic pressure to a higher level than the starting pressure.

Once induction was completed, blood pressure was controlled and stabilized by use of general anesthesia. With the discontinuation of general anesthesia, severe hypertension recurred.

All patients had uneventful recoveries with the exception of patient number seven who expired ten days postoperatively from unexplained reasons. However, he too, until the time of expiration, appeared to be having an uneventful and satisfactory recovery.

From the Departments of Anesthesiology, *City Hospital Center at Elmhurst, Elmhurst, N.Y., and **Albert Einstein College Hospital, Bronx, N.Y.

Reprint requests should be sent to Dr. Sklar, Department of Anesthesiology, City Hospital Center at Elmhurst, 79-01 Broadway, Elmhurst, N.Y. 11373

TABLE I

Patient	Age	Physical Status	Operation	Last blood pressure in ward	First blood pressure in O.R.	Blood pressure lowered to	Blood pressure rose to	Induction agents	Maintenance	Blood pressure in recovery room	Comments	SNP dose μg
1	58	III E	renal artery patch angioplasty	200/100	190/110	90/60	190/110	thiopental 200 mg sch 70 mg	$N_2O—O_2$ halothane-dtc	160/100	medication aldomet 500 mg Q6H minipres 2 mg Q6H lasix 80 mg b.i.d. digoxin 0.125 mg imuran prednisone 30 mg/day post-renal transplant	380
2	38	II E	cesarean section bilat. tubal ligation	120/90	195/105	170/80	200/100	thiopental 250 mg sch 100 mg	$N_2O—O_2$ sch-demerol	160/110	diabetes—no therapy	150
3	67	III E	femoral-popliteal bypass graft	150/100	200/100	110/60	180/120	thiopental 150 mg sch 60 mg	$N_2O—O_2$ halothane	180/100	ASPCVD-digoxin hypertension diabetes temp. pacemaker	150
4	23	III E	cesarean section	180/110	180/110	140/80	190/110	thiopental 250 mg sch 100 mg	$N_2O—O_2$ sch demerol	170/110	Pre-eclampsia est. fetal wgt. 900 grams	250
5	40	III E	cadaver kidney transplant	200/110	180/120	100/60	200/140	diazepam 5 mg thiopental 200 mg sch 80 mg	$N_2O—O_2$ halothane dtc	190/120	chronic renal failure BUN 77 mg % creatinine 9 mg %	120
6	30	III E	cadaver kidney transplant	250/130	220/120	150/90	220/150	thiopental 200 mg sch 80 mg	$N_2O—O_2$ halothane dtc	190/130	chronic renal failure malignant hypertension	910
7	67	IV E	abdominal aneurysmectomy	200/100	205/125	100/60	130/90	thiopental 250 mg sch 100 mg	$N_2O—O_2$ halothane pancuronium	175/130	old myocardial infarction hypertension—no therapy	350

Discussion

All of these patients were scheduled for emergency surgery and were severely hypertensive. If general anesthesia is to be administered to such patients, endotracheal intubation is a mandatory safeguard as it can be assumed that the patient has a full stomach with consequent danger of aspiration. Numerous authors have attempted to prevent the pressor response with partial success (3–5). Recently reported complications emphasize the urgency in treating the acute hypertensive (2). Our patients were all facing extreme risk because of a number of identifiable variables – namely, intraperitoneal or aortic operation, emergency operation, and poor general medical condition (6).

We chose to lower the blood pressure acutely with sodium nitroprusside. Siedlecki (7) utilized trimethaphan and found that it completely prevented an increase of arterial pressure above the initial value during intubation. This study, however, was with normotensive patients, and the trimethaphan infusion was continued as long as the ninth minute of general anesthesia. It was feared that the potential for an accentuated hypotensive action is possible during the time of injection of thiopental and, therefore, the sodium nitroprusside infusion was discontinued. Additionally, trimethaphan was not utilized since various investigators have demonstrated prolonged neuromuscular blockade with a trimethaphan-succinylcholine sequence (8, 9). Sklar and Lanks (10) investigated the interaction of trimethaphan and sodium nitroprusside on hydrolysis of succinylcholine in vitro. They found trimethaphan to be a potent noncompetitive inhibitor of pseudocholinesterase, which would prolong the action of succinylcholine and neuromuscular blockade. On the other hand, sodium nitroprusside had no inhibitory effect in vitro, and there have been no reports relating sodium nitroprusside to prolonged paralysis. Thus, we feel sodium nitroprusside is the superior drug in this situation.

It should be noted that sodium nitroprusside infused with thiopental sodium and succinylcholine in the sequence described, could not block the pressor response to laryngoscopy and intubation. Blood pressure rose to preinduction levels that the patients could presumably tolerate. More severe rises, however, might have been dangerous.

Laryngoscopy accomplished with the aid of topical spray will certainly lead to a similar pressor response (7). Stoelting recommended attenuating pressor responses when laryngoscopy and intubation are likely to take more than 30 seconds, particularly in patients with coronary artery disease or intracranial hypertension (11). We agree, but feel that such a time limit as a criterion for attenuation is unrealistic, and would prefer that all severely hypertensive patients have their pressure lowered as the duration of laryngoscopy is not always predictable. Interestingly, Hamilton (12) editorialized in favor of hypotension, myocardial depression and work reduction for the heart with consequent reduced myocardial oxygen demand. We utilized halothane in five of our seven patients, and narcotic analgesia only in the two cesarean sections. Once the endotracheal tube is in place with the cuff inflated, a potent inhalational agent is an excellent hypotensive agent. Halothane's relaxant effect on the uterus precluded its use in the cesarean sections and presumably methoxyflurane would have been a better choice.

Glass (13) recommended a dosage schedule for sodium nitroprusside of not more than 10 μg/kg/min. The largest dose any patient received was 910 μg over five minutes. This patient weighed 68 kg and received a dose of 2.6 μg/kg/min which is well within Glass' guidelines to prevent nitroprusside toxicity. Additionally, Vesey et al (14) recommended not using more than 1.5 mg/kg during short-term infusions. The dosage required in the circumstances we have described are certainly within all guidelines enunciated.

The rapid hypertensive response surprised us as we believed that the sodium nitroprusside was still acting. Several reports indicate that there is a grace period following cessation of the sodium nitroprusside infusion until blood pressure returns to normal (15, 16). This may not, however, be true when the patient is challenged with the potent stimulus of intubation. We hesitate to recommend larger doses, as we feel dosage of this drug must be critically monitored and the rate of infusion must be controlled by a pump within guidelines of the recommended dosage. Alternatively, the nitroprusside infusion could be continued during laryngoscopy and intubation. Whether this would be more effective we cannot predict, but we chose to discontinue the drug as it was being followed by another hypotensive agent, thiopental.

Though we recommend the management of hypertensive patients for emergency surgery with the method described, we feel that therapy with sodium nitroprusside should be restricted to this group. We suggest that, for elective surgery, hypertensive patients be treated medically until their blood pressure is controlled and they are in the best possible condition for anesthesia and surgery.

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Nonfatal Amniotic Fluid Embolism: A Case Report of Post-partum Respiratory Distress with Histopathologic Studies

WALTER G. WASSER, M.D., SIDNEY TESSLER, M.D., CHOLPADY P. KAMATH, M.D., AND
ALAN J. SACKIN, M.D.

Abstract

Respiratory distress and hypotension occurred in a 23-year-old primipara two hours after Caesarian section. Fever and diffuse alveolar infiltrates persisted for several days, but diminished after the onset of glucocorticoid therapy. One month later, an open lung biopsy confirmed a diagnosis of amniotic fluid embolism. This represents pathologic confirmation of the syndrome in a surviving patient.

With the decrease in deaths caused by infection, hemorrhage, and eclampsia, amniotic fluid embolism (AFE) is emerging as a common cause of obstetric maternal mortality (1,2). This syndrome is characterized by respiratory distress, shock and hemorrhage from intravascular coagulopathy and may follow intrauterine fetal death, abruptio placenta or uterine rupture (3). Until recently, this disease has been considered invariably fatal. Increasing evidence has suggested that AFE may, occasionally, not result in death but, rather, may lead to postpartum respiratory failure. Evidence supporting the diagnosis of AFE in these cases has been the finding of squamae or lanugo hair in the maternal sputum or blood obtained from a central venous catheter (4,5). The following case describes pathologic confirmation by open lung biopsy of nonfatal amniotic fluid embolism.

Case Report

A 23-year-old, para 0000 at term after a normal pregnancy was admitted with mild contractions. Examination revealed −3 station and a 2 cm cervix. Her membranes spontaneously ruptured four hours later; clear fluid leaked freely. Vital signs including fetal heart rate were normal. An oxytocin infusion was started seven hours after admission but terminated one hour later when meconium staining was noted. Labor failed to progress; a Caesarian section was performed 14 hours after admission under general anesthesia. A healthy infant was delivered, the placenta was extracted and uterine lacerations were repaired.

Two hours after delivery, the patient became dyspneic and cyanotic. The blood pressure was 80/60 mm Hg, the pulse was 124 per minute and regular, the respiratory rate was 40 per minute, and the temperature was 36.2° C rectally. Physical examination revealed diffuse rhonchi, bibasilar rales and an accentuated pulmonic second sound. Arterial blood gases showed a pH of 7.47, a PaO2 of 32 torr and a PaCO2 of 31 torr. A chest roentgenogram revealed bilateral alveolar infiltrates (Fig. 1). The white blood cell count was 31,600 per mm^3 with 3% metamyelocytes and 39% band forms. The prothrombin time, partial thromboplastin time, thrombin time, fibrinogen and fibrin split products were within normal limits.

Treatment for aspiration pneumonia with hydrocortisone 500 mg, ampicillin 12 gm daily, and humidified oxygen was given. Glucocorticoid dosage was reduced over the four days. On the fourth hospital day, the rectal temperature rose to 38.2° C. Cultures of blood, urine and sputum that had been obtained prior to treatment revealed no growth. Chest roentgenogram showed increasingly confluent alveolar shadows. The ampicillin was discontinued and penicillin, nafcillin, and gentamicin was begun.

The temperature rose to 39° C on the seventh day. The PaO2 on an FIO2 of 0.3 was 51 torr. Since the clinical features were compatible with AFE, prednisone 80 mg daily was initiated. The patient defervesced gradually and became afebrile on the tenth day. Reduced alveolar

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From the Departments of Medicine and Pathology, Maimonides Medical Center, Brooklyn, N.Y. 11219.

Requests for reprints should be sent to Dr. Tessler, Maimonides Medical Center, 4802 Tenth Ave., Brooklyn, N.Y. 11219.

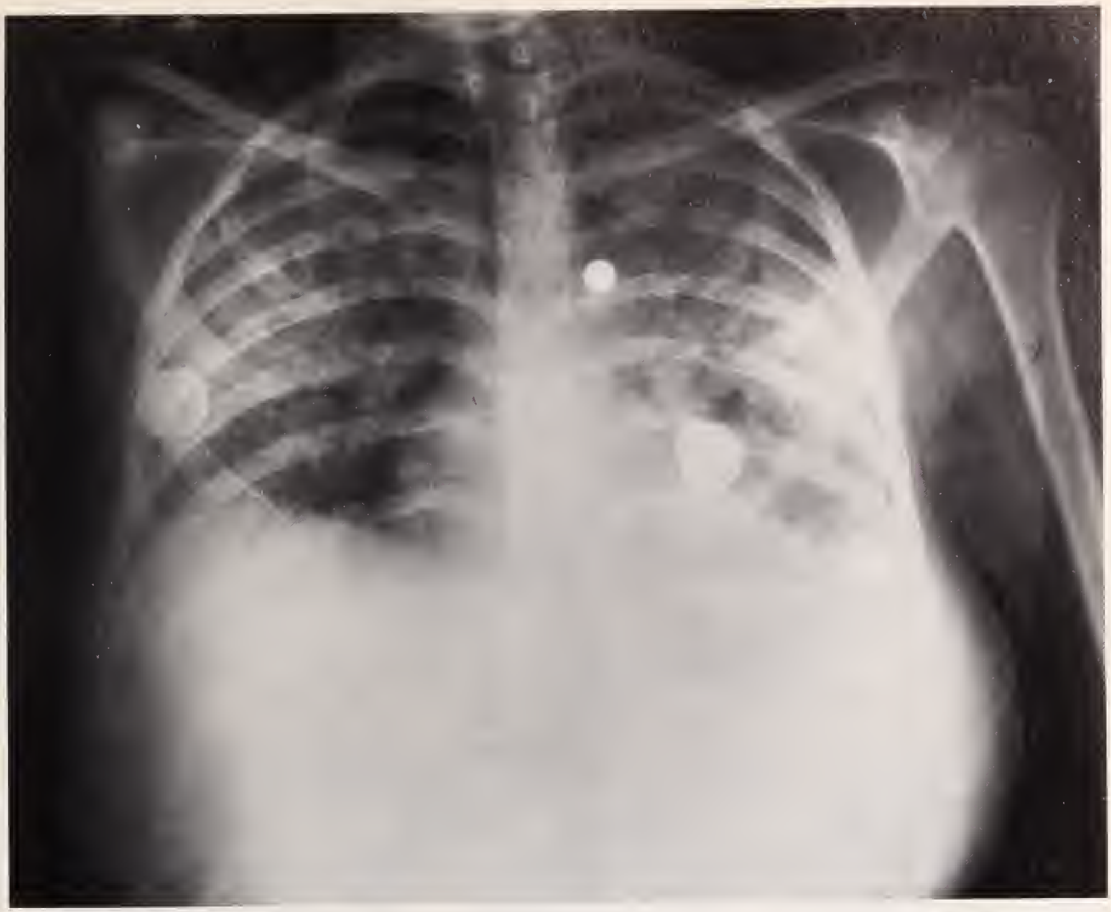

Fig. 1. Chest roentgenogram taken four hours after delivery showing diffuse alveolar infiltrates.

nfiltrates on chest roentgenogram were noted on the 16th day.

On the 23rd day, the infiltrates had cleared. Due to ersistent cyanosis on minimal exertion and a resting PaO2 of less than 65 torr on room air after several days, n open lung biopsy was performed on the 33rd day. On he 40th day the patient was noted not to be dyspneic on xertion and a resting PaO2 on room air was 80 torr. She vas discharged on Prednisone 25 mg daily. The patient as been asymptomatic over a one year follow-up period.

Histopathology

Open lung biopsies were obtained from the lower lobe nd the lingula of the left lung. Microscopically, both pecimens showed a similar disease process. There were umerous nodular lesions involving the alveolar septa Fig. 2a, 2b). These were composed of lymphocytes, istiocytic cells with slightly basophilic granular cytolasm, and round to elongated nuclei, some extracellular ranular debris, and occasional keratotic squamae. The odules also contained abundant acid mucopolysaccha-ide as shown by positive staining with alcian blue (pH .0) and negative staining with mucicarmine.

Discussion

Manifestations of AFE include respiratory distress, cyanosis, and hemorrhage caused by intravascular coagulopathy and shock. These symptoms may progress to coma and death within minutes (3). The postmortem histologic diagnosis of AFE consists of demonstrating epithelial squamae, lanugo hair, fat emboli derived from vernix caseosa, and mucin in the arterioles of the lung (3). Roche and Norris have shown that mucin, probably derived from fetal meconium, stains specifically for acid mucopolysaccharide (6). The mucinous component of amniotic fluid is not only important in the histochemical diagnosis of AFE, but is thought to be a critical factor in its etiology as intravenous injection of amniotic fluid filtered to remove mucin will not produce the clinical features of this syndrome (7).

Only 25 cases have been reported in the English language medical journals as probable survivors of AFE. These patients manifested postpartum respiratory distress and cyanosis and half showed a coagulopathy significant enough to lead to hemorrhage. Diagnosis of AFE was demonstrated in only three cases. In one, fetal squa-

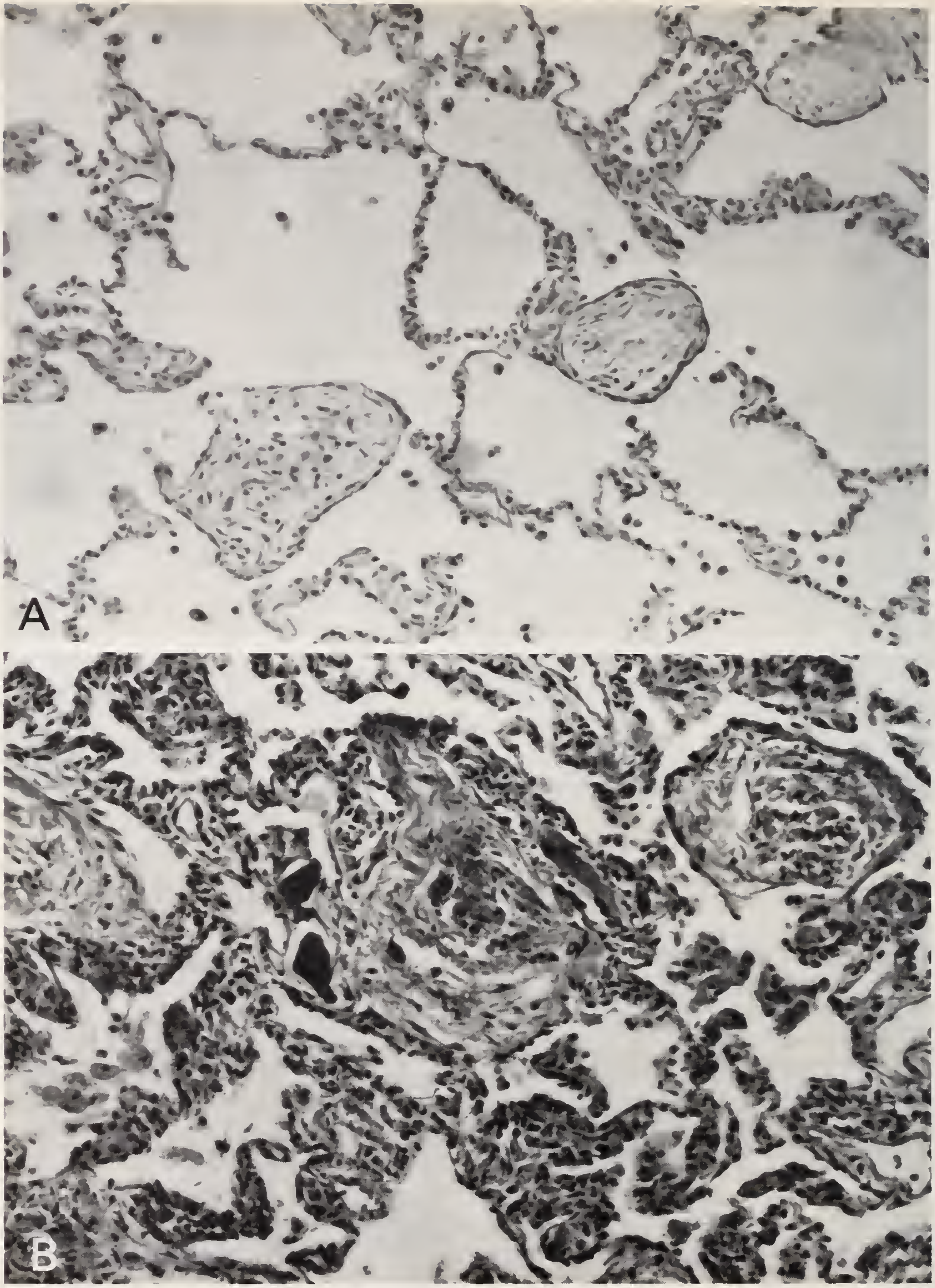

Fig. 2a. Low power view of open lung biopsy showing numerous nodular lesions involving the alveolar septae (Hematoxylin and eosin × 40 original magnification).

Fig. 2b. High power view of the nodules showing lymphocytes, histocytic cells with round to elongated nuclei, some extracellular debri and occasional keratotic squamae. (Hematoxylin and eosin × 10 original magnification).

mae were noted in the sputum (4). In the other two cases, mucin and cellular debris were noted in the buffy coat of central venous blood (5,6).

Our patient demonstrated a protracted postpartum acute respiratory failure without coagulopathy. Prolonged fever with negative cultures and a leukemoi reaction were also features. Following defervescence an normalization of the chest roentgenogram, hypoxemi and persistent cyanosis on exertion led to an open lun biopsy that yielded pathologic evidence for AFE.

Administration of glucocorticoid was followed by defervescence in three days and clearing of the chest roentgenogram in eight days. Although one may infer a salutary effect in our patient, the role of glucocorticoids in the treatment of AFE is in need of further clarification.

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Rhabdomyomas: A Rare Cause of Unilateral Proptosis

Yosef P. Krespi, M.D.*, Peter M. Som, M.D.**, and Joel M. A. Shugar, M.D.*

Abstract

Rhabdomyoma is a benign tumor of mature striated muscle cells. Orbital rhabdomyomas are very rare, with only five case having been reported in the world literature. We are presenting the sixth case and the first one arising from the medial rectu muscle.

Case Report

The patient was a 31-year-old oriental male with a five-month history of blurred vision, mild proptosis and limitation of motion of the left eye. Six weeks prior to admission he developed pain, sometimes severe, behind and slightly to the left of the bridge of the nose.

The pertinent physical findings were visual acuity OD 20/20, OS 20/30. The visual fields were normal on the right and there was a left temporal field defect with a central scotoma. There was marked unilateral papilledema, and paresis of the left medial rectus was noted. The remaining physical and laboratory findings were unremarkable. A left carotid angiogram revealed displacement of the ophthalmic artery around a medial mass (Fig. 1). No abnormal vascularity was noted and there was no tumor blush. A CT scan (Fig. 2a, 2b) revealed a mass lesion in the region of the medial rectus muscle that showed enhancement after the administration of contrast material. The patient underwent a lateral rhinotomy and external ethomoidectomy. The lamina papyracea was removed with the superior limit at the level of the ethmoid vessels, and with the inferior limit at the level of the lacrimal fossa. The periorbital fat was removed and the medial rectus muscle was identified. The displaced vessel on the angiogram was identified and preserved. A 1.5 × 2.0 cm encapsulated tumor was removed from the medial rectus muscle.

The specimen was completely encapsulated. It wa composed of striated muscle fibers with some interstitia fibrous tissue (Fig. 3). Occasional aggregates of lymphocytes and plasma cells were present. Postoperatively, th patient had full return of extraocular muscle functio and is asymptomatic at two-year follow up.

Discussion

Rhabdomyomas usually are seen clinically as progressive, irreducible, and unilateral proptosis. They occu most often in young adults. The first reported case wa by Jennings in 1895 (1, 2). His patient was a 14-month-old baby. One year later, Alt reported a second case occurring in the palpebral muscle of the eyelid (1, 2).

The third case was reported by Wible in 1918 in a 29-year-old female with a history of proptosis (3). A firmly fixed hard mass was found pushing the eye upward and medially. She required an orbital exenteration.

The fourth case was in a teenager with a seven-yea history of unilateral exophthalmus. At surgery, a 3 × 1.5 cm tumor of the superior rectus muscle was found (4).

The fifth case arose in the inferior rectus muscle and was removed by a lateral orbitotomy (5).

Histologically these tumors have thick outer fibrous capsules, striated muscle fibers with interposed fibroelastic tissue and focal aggregations of lymphocytes and plasma cells. Muscle cells are imperfectly formed with no sarcolema and deficient striations.

Pathologists differ as to whether these represent true neoplasms. Calhoum classifies them as pseudotumors when focal collections of inflammatory cells are present and mixed tumors when they contain fibrous and/o nerve tissue in addition to adult muscle tissue (6).

From the Departments of Otolaryngology*, and Radiology**, The Mount Sinai Hospital and Mount Sinai School of Medicine of the City University of New York, N. Y. 10029.

Requests for reprints should be sent to: Yosef P. Krespi, M.D., Department of Otolaryngology, The Mount Sinai Hospital, New York, N. Y. 10029

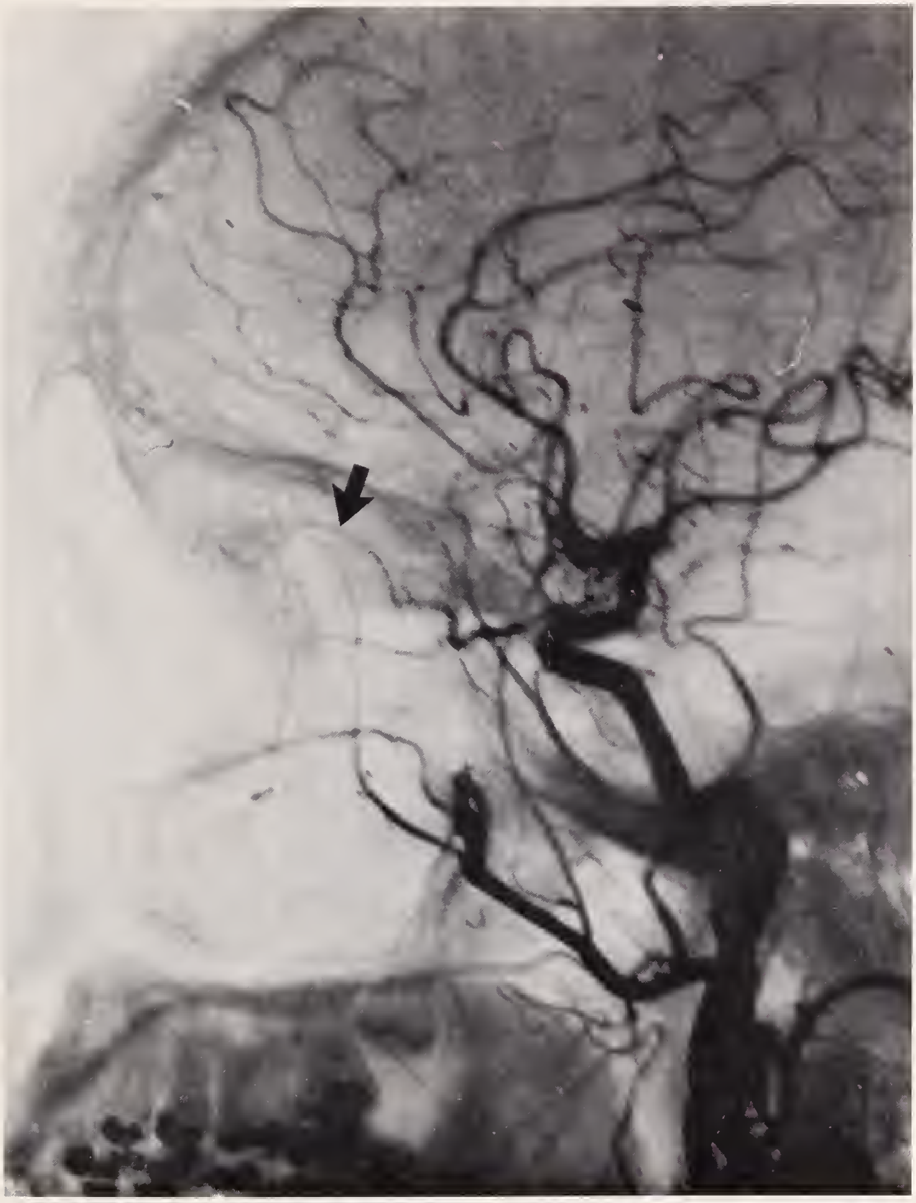

FIG. 1. Lateral carotid arteriogram reveals displacement of ophthalmic artery (arrow) by an avascular mass.

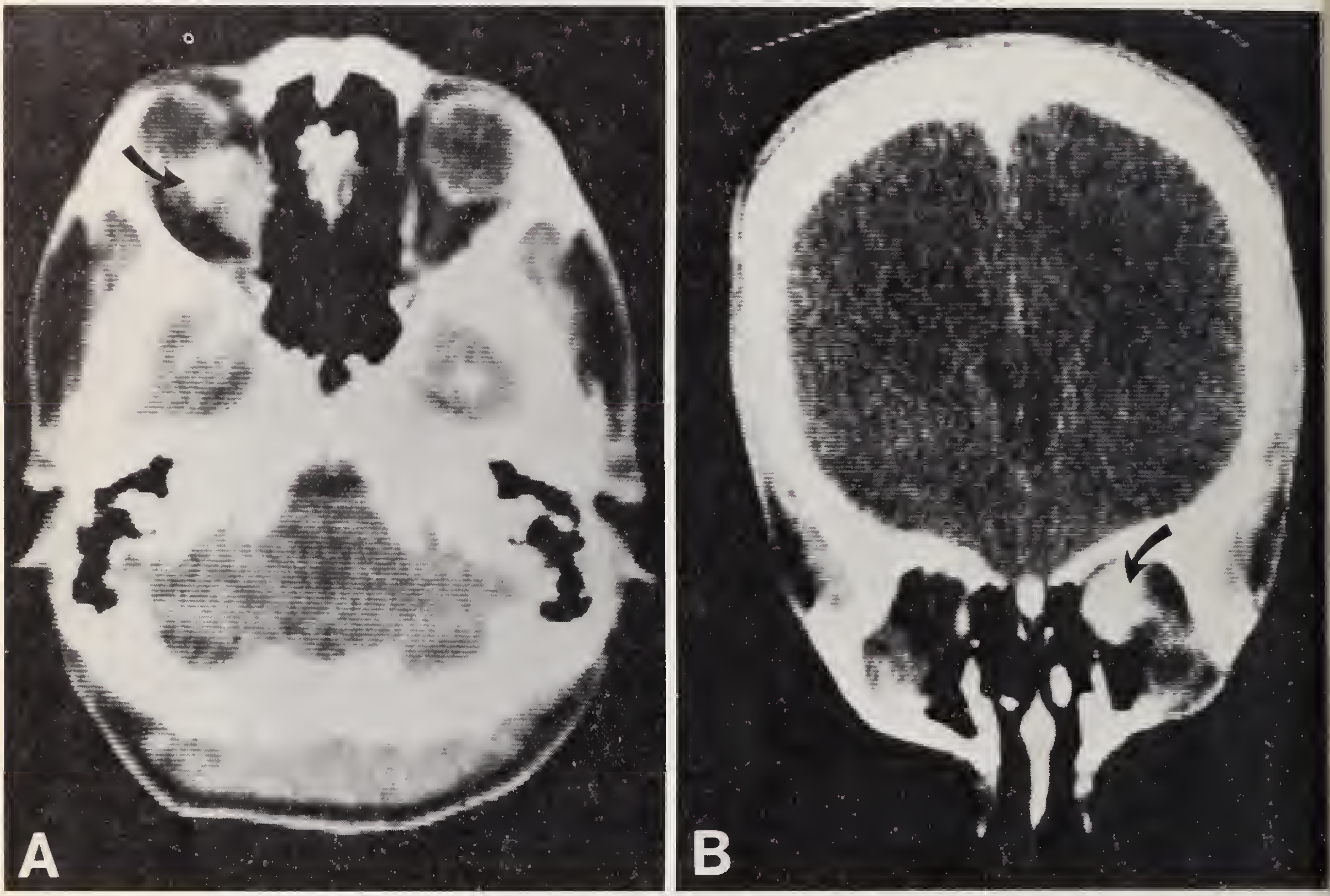

Fig. 2a. Axial CT scan reveals an enhanced mass in the mid and posterior medial left orbit (arrow). There is no bone destruction.
Fig. 2b. Coronal CT scan reveals the supero-medial position of the enhanced mass in the left orbit (arrow).

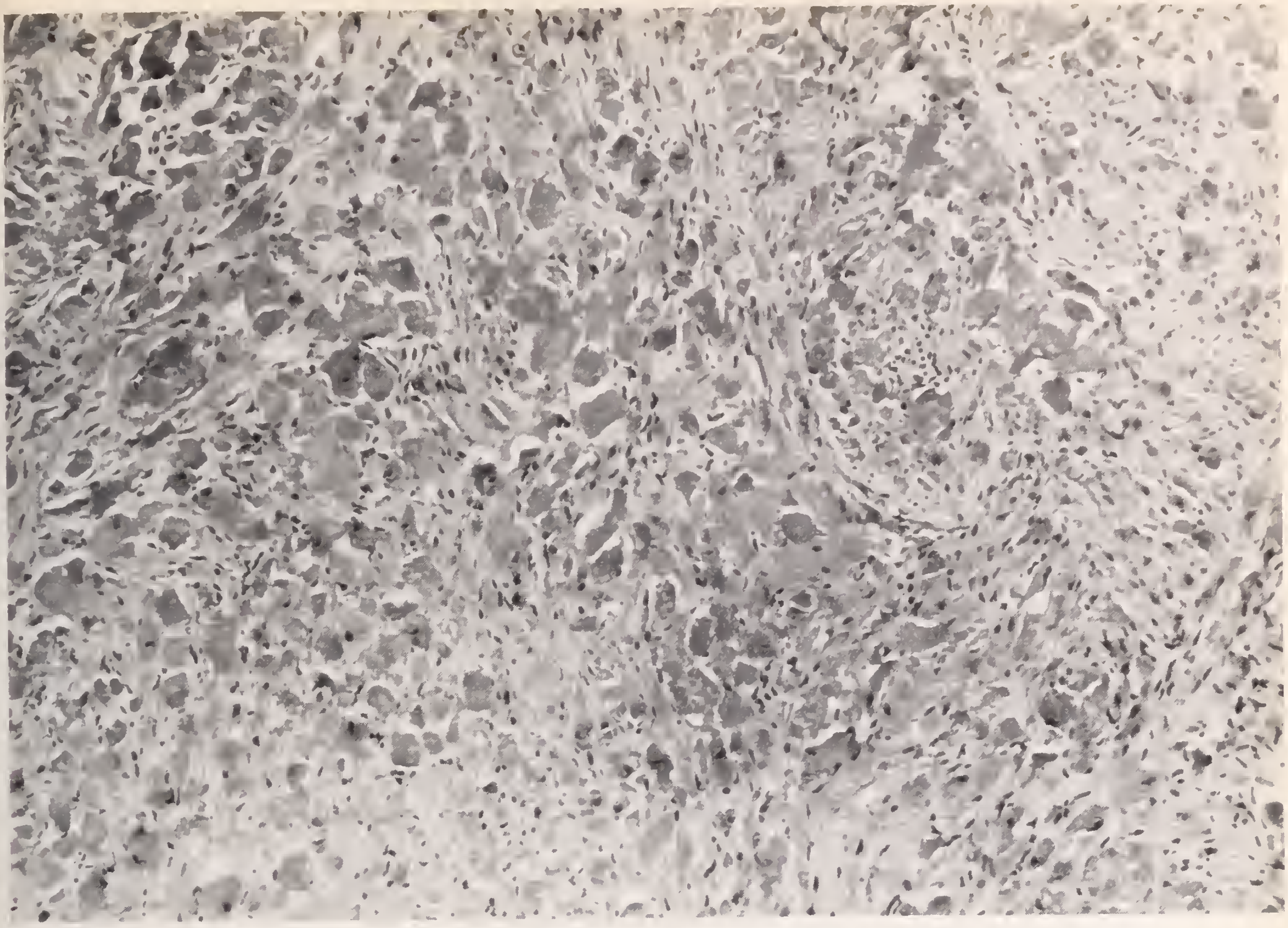

FIG. 3. Photomicrograph reveals striated muscle fibers with focal aggregations of lymphocytes and plasma cells.

Focal aggregations of lymphocytes and plasma cells may be present in many cases, including ours (3, 5). Because of this, some pathologists refer to these cases as productive myosities rather than rhabdomyomas.

The differentiation between rhabdomyomas and orbital rhabdomyosarcomas is difficult. Both occur primarily in the younger age groups. The lack of bone destruction might indicate a rhabdomyoma; however, an early rhabdomyosarcoma can also appear without bone destruction. Differentiation on CT Scans and arteriography is virtually impossible–particularly with the early localized sarcomas. The lack of demonstrated tumor vessels or neovascularity on arteriography and a "tumor blush" seen on CT scan is not a rare occurrence and is explained by the contrast material pooling in extravascular tumor compartments rather than contrast accumulation in tumor vessels. The final diagnosis rests with the pathologists. This case is presented to demonstrate that, although rare, this benign tumor must be included in the differential of unilateral proptosis.

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Hypercalcemic Coma Secondary to Tamoxifen Citrate

MIRJANA VALENCIC, M.D., DAVID WOLDENBERG, M.D., AND BERNARD KABAKOW, M.D., F.A.C.P.

Tamoxifen citrate, a new nonsteroidal antiestrogen, has recently become available for general use in the treatment of metastatic breast carcinoma, particularly in those women with estrogen-receptor positive assays of their tumor or evidence of previous hormonal responsiveness. Overall clinical response rates have ranged between 22 and 50% (1). The relative lack of toxicity of this new compound has been seen as its greatest attraction with only occasional nausea, hot flushes, skin rash and blood count depression having been reported. More recently, cases of hypercalcemia in the early phases of treatment have been reported (2). We describe here a patient who developed life-threatening hypercalcemia with a serum calcium level of 20.7 mg/dl after ingesting only eleven 10 mg. tablets of tamoxifen.

A 67-year-old white female developed right-sided headaches in July 1977. She had a left modified radical mastectomy for carcinoma in 1974 but the tumor tissue was not sent for estrogen-receptor. The pathology report read "infiltrating duct cell carcinoma measuring 6 × 5 × 6 cm with 25 lymph nodes negative for tumor." No postoperative radiation or chemotherapy was given. A bone scan in February 1978 revealed multiple areas of increased uptake in the skull and thoracolumbar spine and skeletal x-rays confirmed the presence of osteolytic metastases in these areas. A CAT brain scan was negative. She was seen in consultation on February 21, 1978, and was started on tamoxifen citrate 10 mg p.o., b.i.d. A complete blood count was normal and blood chemistries revealed a serum calcium of 10.1 mg/dl, phosphorus of 3.8 m/dl, a serum albumin of 4.3 g/dl, total protein of 7.3 g/dl, an alkaline phosphatase of 455 International units, and a blood urea nitrogen of 16 mg/dl. Over the next five days she developed nausea, anorexia and weakness. This progressed to lethargy and she was admitted to Beth Israel Medical Center in a comatose state. She had taken eleven tablets of tamoxifen over 5½ days. The othe medication that she had taken included tylenol with codeine, bufferin and indomethecin. Physical examination on the admission revealed a comatose female, dehydrated, with evidence of a left mastectomy scar. Th heart was not enlarged, regular sinus rhythm, no murmurs; the lungs showed scattered bilateral rales. Th abdomen was soft with the liver palpable 2 fingers below the right costal margin. The serum calcium on admission (done in duplicate) was 20.7 mg/dl. An electrocardiogram revealed a regular sinus tachycardia 100/minute. The T waves were flattened in most leads except $V_2 - V_4$ where the QT interval corrected for rate (QT_C) measured 0.2 seconds (N − QT_C = 0.32 to 0.35 seconds). U waves were seen in some of the leads as well. These findings were consistent with the diagnosis of hypercalcemia. She wa treated with vigorous saline hydration, furosemide, corticosteroids and intravenous mithramycin. After 16 hours she became more responsive and her serum calcium returned to normal. At that time, her serum calcium was 13.1 mf/dl, a parahormone level was 235 pg/ml. The patient has subsequently been treated with intravenous 5-fluorouracil, methotrexate and vincristine and oral cytoxan, halotestin and prednisone. She was also given radiotherapy to several metastatic bony areas. Her serum calcium has remained normal on this regimen and her bone scan has shown improvement.

The treatment of metastatic breast cancer with androgens, estrogens and progestins can result in hypercalcemia, associated with an apparent flare of tumor (3) Tamoxifen which belongs to the triphenylethylene class of compounds is a potent antiestrogen in rats and monkeys but behaves like estrogen in mice. Higher doses of tamoxifen in humans may have estrogenic activity. In addition, females treated with antiestrogens that can block estrogen-receptors, manifest a rise in gonadatropin secretion and this, in turn, can increase estrogen levels. In rats, tamoxifen can cause glycogen accumulation and increased uterine weight, both of which are seen with estrogen treatment (4, 5). These factors may be responsible for the hypercalcemia and tumor flare described in

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From the Division of Hematology-Oncology, Department of Medicine, Beth Israel Medical Center, New York, N.Y. 10003 and Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

our patient and others. The other possibility is that tamoxifen may cause hypercalcemia by a direct action on bone regardless of its estrogen-like effects. Our patient was unusual in that she was well hydrated and fully ambulatory at the start of tamoxifen therapy and ingested only eleven tablets (110 mg. total) over a 5½ day period. Other studies of hypercalcemia associated with tamoxifen have reported longer periods of tamoxifen administration, usually several weeks before the hypercalcemia became manifest (6). Caution and careful observation with frequent monitoring of serum calcium should be practiced in the administration of tamoxifen.

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The Association of Lymphocytic Interstitial Pneumonia and Systemic Lupus Erythematosus

BARRY BENISCH, M.D. and BERNARD PEISON, M.D.

Abstract

A case of lymphocytic interstitial pneumonia (LIP) occurring in a patient with systemic lupus erythematosus (SLE) is described. Although LIP is commonly associated with Sjogren's syndrome, this is believed to be the first report of its association with SLE. The association of interstitial pneumonia (UIP) and various lymphomas with SLE has been the subject of several reports. The present case in concert with these reports raises the possibility that an altered immune response may play a role in the pathogenesis of these disorders.

Introduction

Lymphocytic interstitial pneumonia (LIP) is a morphological subdivision of interstitial lung disease considered by some authors to represent a premalignant state (1,3). It is characterized, radiologically, by bilateral lower lobe infiltrates and, histologically, by a pleomorphic lymphohistiocytic infiltration of the pulmonary interstitium. The infiltrates contribute to form a spectrum of findings ranging from widened septa to confluent masses indistinguishable from pseudolymphoma. The association of LIP with Sjogren's syndrome and rheumatoid factor is well documented (4).

Systemic lupus erythematosus, although occasionally associated with usual interstitial pneumonia (UIP) and various lymphomas has, to our knowledge, not been described coexisting with LIP (5–10). The purpose of this report is to describe such a case and speculate about its significance.

Case Report

The patient was a 55-year-old white female with known systemic lupus erythematosus of 15 years duration. SLE was manifested by a butterfly rash, arthalgias, intermittent proteinuria and serositis. L.E. tests, ANA and anti-DNA antibodies were repeatedly positive. Serum protein electrophoresis showed a polyclonal gammopathy. At no time did she show either keratoconjunctivitis sicca, xeropthalmia or xerostomia. On her last admission, she had bilateral basilar reticular infiltrates on chest x-ray and fever (Fig. 1). Blood cultures grew Citrobacter freundii. The patient expired shortly thereafter.

Necropsy revealed diffuse infiltration of the lower lobes, bilaterally, with an admixture of lymphocytes and plasma cells, (Fig. 2) in some areas widening septa (Fig. 3), and in others, obliterating the normal pulmonary architecture. Foci of amyloid which showed the characteristic green birefringence with polarized light after congo red staining were identified (Fig. 4). Poorly defined epithelioid granulomata were scattered throughout as well (Fig. 5). Stains for fungal and acid-fast organisms were negative. No evidence of a lymphoproliferative process was present in any other tissues. Salivary glands were unremarkable.

The remainder of the autopsy revealed acute pyelonephritis with gram-negative sepsis. Findings consistent with systemic lupus erythematosus included polyserositis and focal glomerulonephritis. Immunofluorescent studies were not done.

Comments

Interstitial pneumonias may be classified using histologic criteria as 1) classical or usual interstitial pneumonia (UIP), 2) bronchiolitis obliterans with classical interstitial pneumonia (BIP), 3) desquamative interstitial pneumonia (DIP), 4) lymphoid interstitial pneumonia (LIP), or 5) giant cell interstitial pneumonia (GIP) (4).

From the Department of Pathology, Rahway Hospital, Rahway, NJ 07065.

Requests for reprints should be sent to Barry Benisch, M.D., Rahway Hospital, 865 Stone St., Rahway, N.J. 07065.

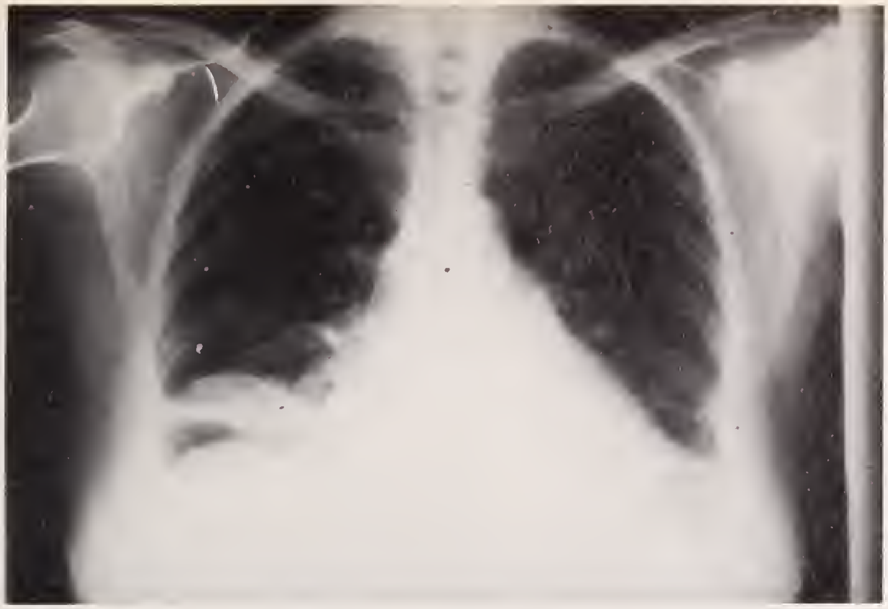

Fig. 1. Chest x-ray showing bilateral lower lobe reticular infiltrates.

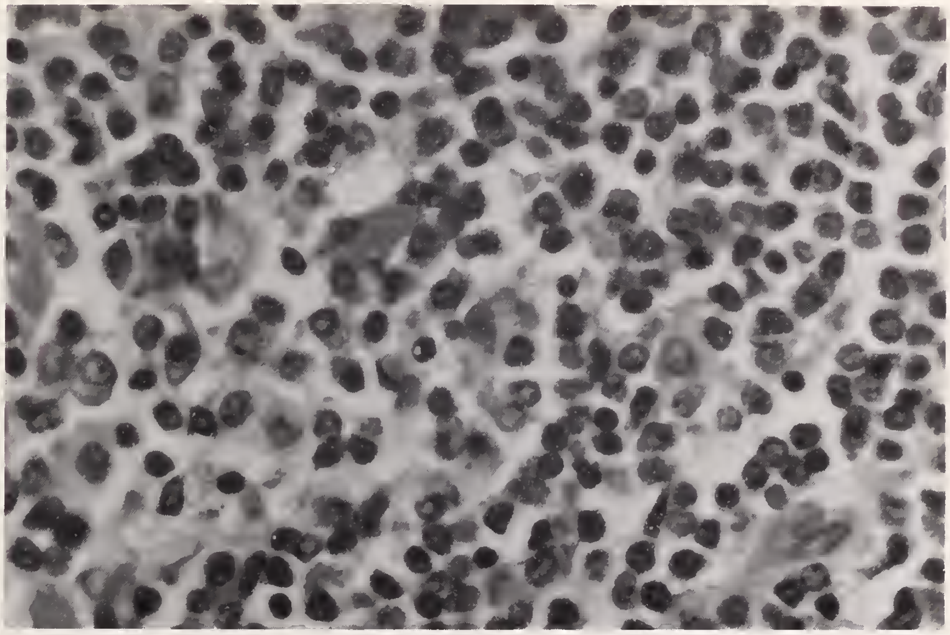

Fig. 2. Photomicrograph of lung showing a lymphohistiocytic infiltrate with scattered plasma cells. Hematoxylin and eosin stain, (× 400).

Despite varied morphology and clinical presentation, all may eventuate in diffuse interstitial fibrosis (4). LIP is characterized histologically by widespread lymphohistiocytic interstitial infiltrates which at one extreme merge imperceptively with pseudolymphoma (1). The natural history is not well defined, but some patients terminate with diffuse interstitial fibrosis as in UIP, and others with malignant lymphoma (2,4). LIP is frequently associated with Sjogren's syndrome and the presence of rheumatoid factor (1). L.E. tests have not been positive in any of the patients reported.

The patient described here was a 55-year-old white female with known systemic lupus erythematosus for 15 years and no evidence of the sicca syndrome. Chest x-rays prior to death revealed bilateral lower lobe infiltrates. At necropsy there was a pleomorphic lymphohistiocytic infiltrate diffusely involving both lower lobes and associated with foci of amyloid and poorly defined epithelioid granulomata, findings characteristic of LIP (1,4,12).

The origin of the pulmonary amyloid in LIP is most likely related to chronic antigenic stimulation with prob-

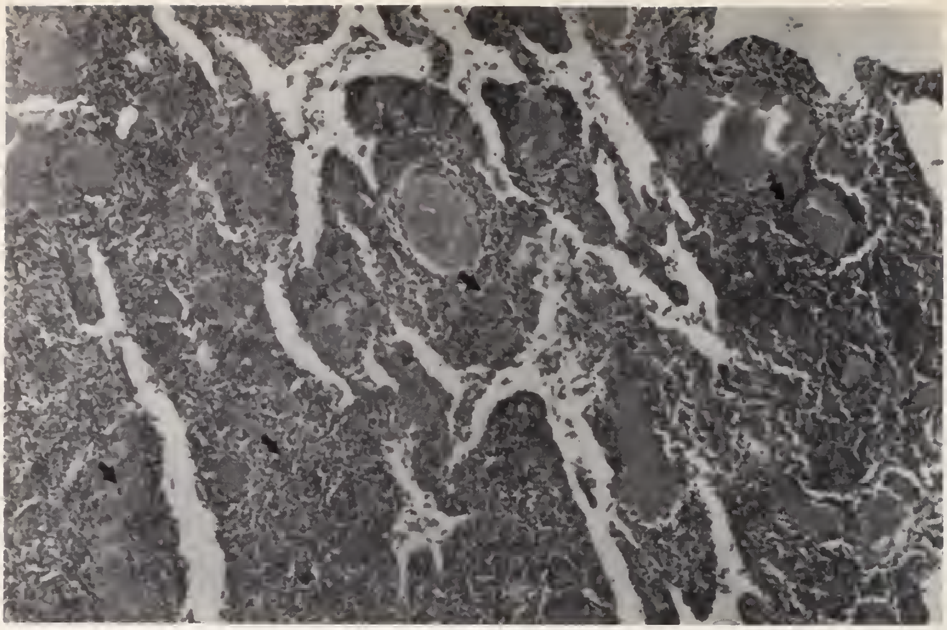

Fig. 3. Photomicrograph of lung showing interstitial lymphohistiocytic infiltrates with markedly thickened septa (arrows). Hematoxylin and eosin, (× 40).

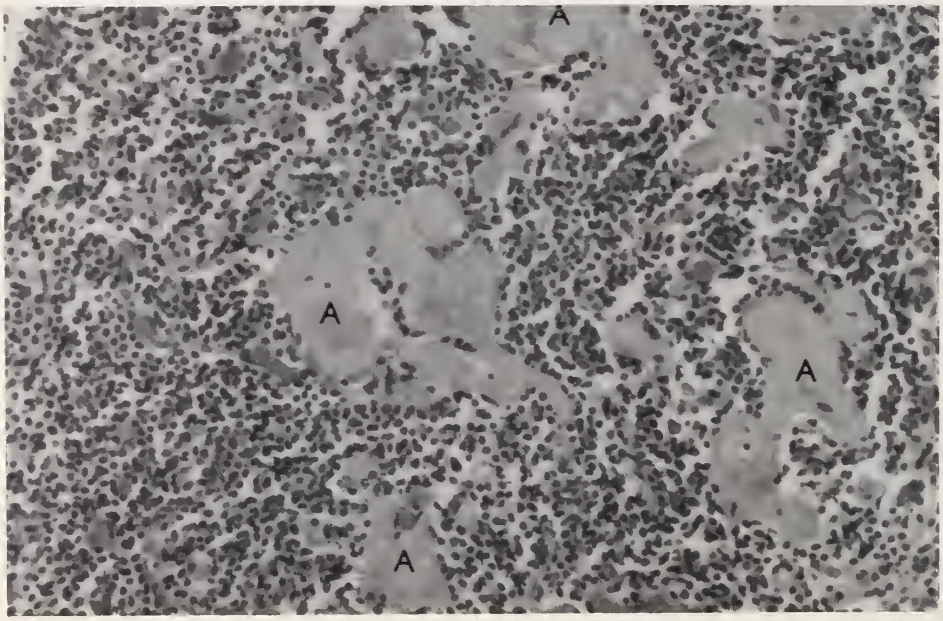

Fig. 4. Photomicrograph of lung showing foci of amyloid (A) lying within a lymphohistiocytic infiltrate. Hematoxylin and eosin, (× 100).

able local production and deposition of altered immunoglobulin. It has an etiology similar to that postulated for the generalized amyloidosis seen in such diverse conditions as rheumatoid arthritis, osteomyelitis and tuberculosis. The epithelioid granulomata, noted in our case and described previously, are not related to areas of amyloid and probably reflect a local state of altered cellular immunity. Lymph nodes, salivary glands and the remainder of the autopsy showed no evidence of a lymphoproliferative process. Although a previous association of LIP and systemic lupus erythematosus has not, to our knowledge, been described, we believe its occurence is not coincidental. The coexistence of UIP and systemic lupus erythematosus has been the subject of several reports and circulating immune complexes and pulmonary deposition of immunoglobulin and complement have been identified in UIP, DIP and LIP (5–7,13). These findings lend some support to the postulate that the observed association of LIP and systemic lupus erythematosus in our case was not fortuitous. Systemic lupus erythematosus has also been described in association with various lymphomas (8–10). Although the signifi-

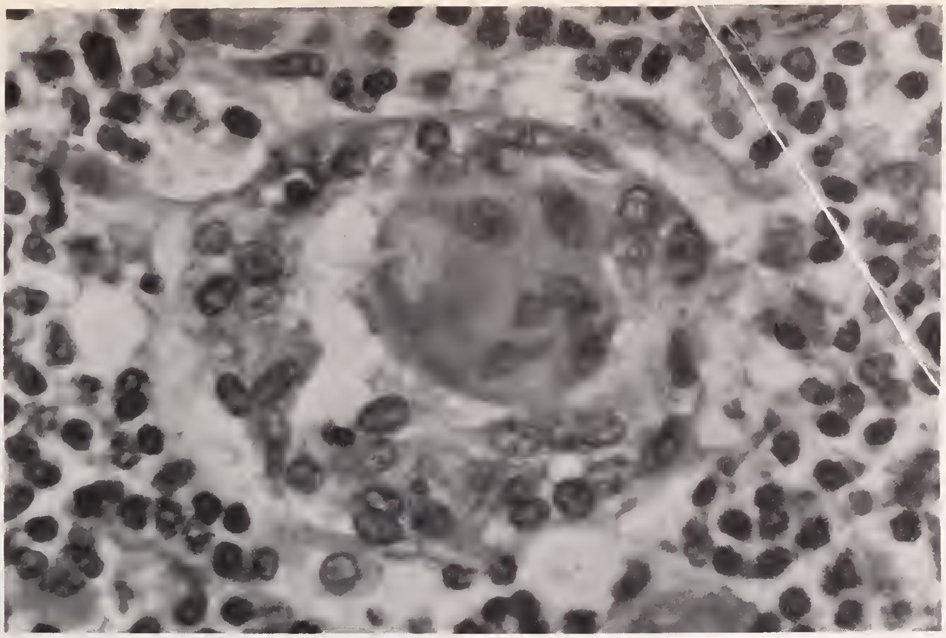

Fig. 5. Photomicrograph of lung showing a loose epitheloid granuloma lying within a lymphohistiocytic infiltrate. Hematoxylin and eosin, (×

cance of these reports is unclear, they may pertain to the present case since LI is considered a prelymphomatous state by some authors (2,3). The etiology of LIP is unknown, but like systemic lupus erythematosus, possible etiologic roles for autoantibodies, genetic or acquired defects in immune surveillance, viruses and delayed hypersensitivity mechanisms have been suggested. Further study of the interrelationship of systemic lupus erythematosus and LIP might provide new insights into the pathophysiology of both disorders.

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Polytetrafluoroethylene (Gore Tex) Graft Interposition in the Dog Common Bile Duct

HARRY SCHANZER, M.D., W. JOHN B. HODGSON, M.D., ROLF OESTREICHER, M.D.,
SANJIVANI BAKARE, M.D., AND A. JAMES McELHINNEY, M.D.

Introduction

Common bile duct surgery is frequently complicated by scar formation at any site of anastomosis. Indeed, late attacks of cholangitis following biliary duct surgery are potentially fatal and require excision of the scar and reanastomosis with concomitant shortening of the duct. Unfortunately, this is no guarantee against further scarring. Furthermore, choledochojejunostomies may suffer the same fate. Clearly, much work remains before these serious problems may be solved.

One approach is to examine the use of prosthetic materials. Past experience with synthetics in the biliary system has not been helpful (1, 2). For any kind of success to be achieved with common bile duct prosthetic interposition, it is necessary to use a substance that has minimum reactivity so that scarring and stricturing is reduced. It should also have a minimum friction coefficient so the flow of bile over it is facilitated and the propensity for stone formation reduced. It was thought that polytetrafluoroethylene (PTFE), having a low reactivity and coefficient of friction, might be a suitable material; therefore, a study of PTFE as a graft interposition in the dog common bile duct was carried out (3).

Materials and Methods

PTFE is made in different sizes. We decided to use the 4 mm internal diameter graft with 5 micron pore size to bridge the dog common duct. Fourteen dogs received this interposed graft. There were five technical failures and the nine remaining dogs were sacrificed at three, eight and fifteen months.

After standard nembutal anaesthesia with the dog supine on the operating table, a midline upper abdominal incision was made. The common bile duct was identified and transected 1 cm above the duodenum after placement of 5-0 tevdek stay sutures. A 2 cm long PTFE graf was then sutured to the proximal and distal stumps o the common duct (Fig. 1). The abdomen was closed wit silk and streptomycin (500 mg intramuscularly) and penicillin (0.5 million units intramuscularly) was given dail for four days starting immediately postoperatively.

The dogs were weighed preoperatively and immediately postoperatively daily. After the first week, weighin took place on a weekly basis. The serum bilirubin wa followed pre- and postoperatively.

At the time of death or sacrifice, autopsy was carrie out with a pathologist who then took the biliary tree fo microscopic study. Blocks were made of the area of th common duct with graft interposition and of the liver. I this way, it was possible to obtain a comprehensive en result.

Results

Fourteen dogs had interposition of a 2 cm length PTF graft in their common duct (Table I). There were fiv failures. Two dogs died within a week. The first one ha biliary leak and peritonitis, and the second dog ha evisceration. Three dogs died with complete commo duct obstruction at six weeks, three months and fou months. These three dogs all suffered weight loss an were remarkable for consistently high levels of bilirubi recorded—up to 8.4 mg%. In one of these dogs no graf was found.

Of the three dogs that were followed for three months two had normal biliary systems and, at the site of th PTFE graft interposition, a complete fibrous sheet ha developed on the outside of the graft. The mucosal linin of the common duct stopped at the graft. The third do had a narrowed area of the common duct near th proximal anastomosis to the graft and a very dilate proximal biliary tree. All three dogs, after an initial drop put on weight and stabilized. The bilirubin levels remained low in all dogs.

In the group that was followed for eight months, on

From the Department of Surgery, Bronx Veterans Administration Medical Center and Mount Sinai School of Medicine of The City University of New York, N.Y.

Requests for reprints should be sent to Harry Schanzer, M.D., Department of Surgery, The Mount Sinai Hospital, One Gustave L. Levy Place, New York, N.Y. 10029.

died of hemorrhagic necrosis of the liver but had a patent biliary tree, no weight loss, and no rise in bilirubin. One dog developed ascites and inanition and weight loss. There was an early postoperative rise in bilirubin to 2 mg% but thereafter the bilirubin level remained below 1 mg%. The prosthesis at sacrifice was lying free in the distal common duct which was obliterated. The third dog had a satisfactory course, without weight loss, but its bilirubin curve showed an early postoperative rise to 1.8 mg%, then a late rise at four months to 3.2 mg% after which the curve returned to normal levels. This dog had much narrowing of the common duct at the proximal anastomosis.

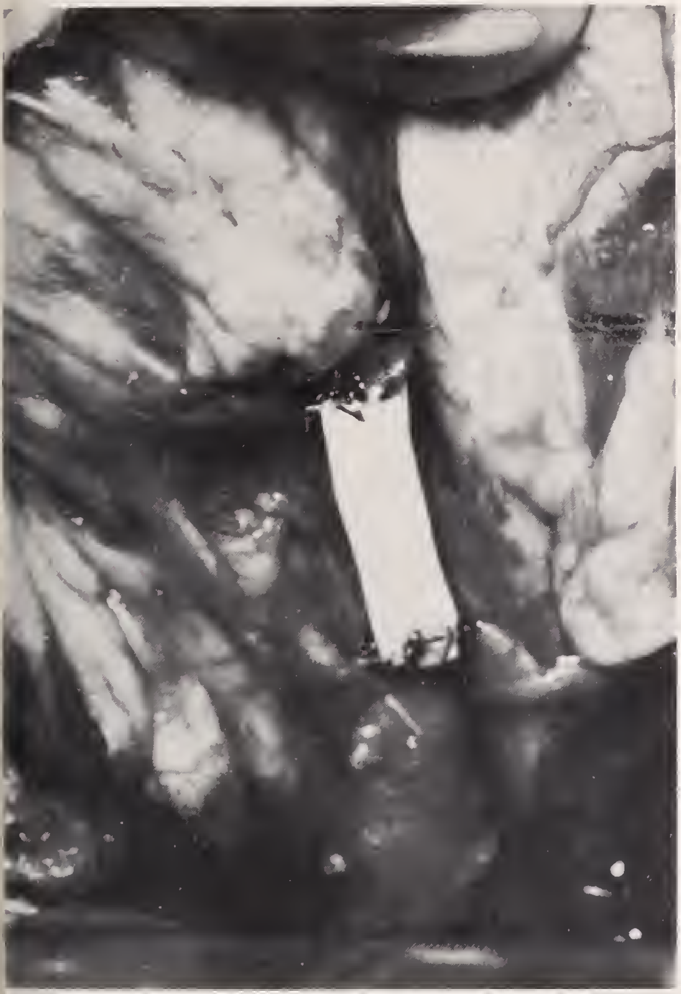

FIG. 1. A 2 cm graft sutured between the proximal and distal stumps of the common duct.

In the third group, followed for 15 months, all dogs remained in good condition throughout. One dog had a normal functioning common duct and graft, with a flat bilirubin tracing. The two other dogs had the prosthesis floating free, with stenosis of the common duct and some proximal dilatation of the biliary tree. The bilirubin curve in one of these dogs showed a postoperative rise to 2.1 mg% and in the other there was a late rise, at four months, to a level of 4.5 mg% after which the bilirubin returned to normal.

Discussion

The search for a practical substitute to restore continuity in the common bile duct has attracted the interest of investigators for many years. Different synthetic and biological tissues have been used with varying degrees of success (4, 14–23). Nevertheless, most investigators have not advocated the clinical application of these methods.

In our study, we chose to use PTFE because of the low reactivity and the low coefficient of friction this material possesses. There was a 50% patency rate for up to 15 months using PTFE in the dog biliary tree. In seven of the nine dogs followed, the PTFE graft was replaced by fibrocollagenous tissue and the graft was usually found lying free in the common duct or expelled through the ampulla. Bilirubin levels of only 3 mg% indicated that stenosis was occurring and indicated that further surgery would be necessary. Excision of the stenosed area alone may have increased the patency rate over long periods of time.

TABLE I

Summary of Results

Dog #	Length of time PO	Result	Autopsy findings
126	6 days	Died	Good graft, evisceration
132	4 months	Died	Complete obstruction CD
162	3 months	Died	Complete obstruction CD
171	5 days	Died	Biliary leak
178	6 weeks	Died	Complete obstruction CD
177	3 months	Sacrificed	Good graft
180	3 months	Sacrificed	Stenosis proximal anastomosis, dilated biliary tree
182	3 months	Sacrificed	Good graft
163	8 months	Died	Good graft, hemorrhagic necrosis liver
165	8 months	Sacrificed	Stenosis distal anastomosis, graft free in CD
166	8 months	Sacrificed	Stenosis proximal anastomosis, dilated biliary tree
106	15 months	Sacrificed	Graft free in CD, mild stenosis proximal anastomosis
142	15 months	Sacrificed	Graft free in CD, mild stenosis proximal anastomosis
157	15 months	Sacrificed	Good graft

In the clinical situation, benign stricture of the bile ducts remains the most serious disease of the biliary tract. Since it occurs as a result of surgery for gallstones, the only truly satisfactory management of stricture is prevention (24).

Once a stricture has occurred, the first attempt at repair has the best chance of success. Smith has had much experience in this field and his methods all include three basic principles (25). The fibrous stricture must be completely excised and mucosal apposition between duct lining and intestinal mucosa is essential. The anastomosis should be as large as possible and without tension. An enteroanastomosis should be constructed if there is any danger of ascending cholangitis from contamination of bowel contents entering the biliary system.

However, the clinical situation is not always ideal. It is not always possible to bypass scar tissue. Then, stents or tubes must be used. Sometimes they can be used with success and survival with a tube in place for as long as 25 years has been reported (24). It is in these cases that there may be a clinical application for a graft interposition. In our experience with PTFE with a 5 micron pore size the fact that 50% of the dogs had late stricture precludes its use in the clinical situation.

Summary

The possibility of interposing a PTFE graft in the common duct was studied in 14 dogs. Five dogs died in the first six weeks after surgery, secondary to technical complications. The nine remaining dogs were sacrificed at three, eight and fifteen months after surgery. Four dogs had a good graft with normal biliary tree. Two dogs had the graft free in the common duct with mild stenosis of the proximal anastomosis. Three dogs had severe stenosis in one of the anastomoses with marked dilatation of the biliary system. From this experience, it is concluded that the clinical use of PTFE graft in the common duct cannot be advocated.

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Pedunculated Endocardial Polyps in Rheumatoid Valvulitis Producing Arterial Embolization

CHING-SHEN LIN, M.D. AND FREDERICK G. ZAK, M.D.

Abstract

A rheumatoid patient suddenly developed femoral arterial embolization and died after surgery. The autopsy showed rheumatoid granuloma in the mitral ring with several endocardial thrombi which were the source of embolization.

Introduction

Cardiac involvement by rheumatoid granuloma was first reported by Baggenstoss and Rosenberg in 1941 (1). Since then, many cases have been diagnosed at autopsy and reported. Three to five percent of cases of rheumatoid disease are accompanied by granuloma formation (2, 3). Clinically, these cases may show heart block, aortic stenosis or insufficiency, mitral insufficiency or no symptoms at all.

It is our purpose to report a unique case of arterial embolization of the leg from pedunculated mural thrombi that arose from a rheumatoid granuloma of the mitral ring.

Case Report

This 58-year-old woman was admitted to Methodist Hospital for the second time because of sudden coldness and cyanosis of her left leg.

She had an episode of rheumatic fever without any equel at the age of 24. For the past 20 years, she suffered rom pain in the joints and deformities of the fingers and oes and was placed on triamcinolone (Aristocort). She ecame bedridden four years ago. She smoked cigarettes nd recently used two pillows for sleep. She was allergic o penicillin and codeine.

The patient was admitted to Methodist Hospital for the first time on July 6, 1975, because of ecchymosis of the skin over the left arm and also for further evaluation of her joint pains and deformities of fingers and toes. While she was able to wash and dress herself, she was unable to turn on her television set. On examination, besides ecchymosis and deformities of fingers and toes, she had deformity of the sternum with forward protrusion and kyphosis of the thoracic spine. Her heart and lungs were normal. Psoriasis was seen on her face and abdomen. No subcutaneous nodules were seen. Hemogram, coagulation profiles and blood chemistries were all within normal limits except for a slight increase in serum alkaline phosphatase and lactic dehydrogenase. Radiologic examination showed severe osteoporosis of hands and feet with marked narrowing of tarsal and interphalangeal joint spaces. She was given physical therapy. During hospitalization, she had a sprain of her right ankle which was complicated by swelling. There was also an episode of vomiting with fever for which ampicillin was given. The patient was discharged, under home care, six weeks after admission on tylenol and methyl prednisolone.

She was readmitted 18 days after discharge from her first admission because of fever, pain, swelling and coldness of her left leg of two days' duration. She had vomited twice but did not have jaundice. On examination, her blood pressure was 100/60 mm Hg and her pulse rate was 112 per minute. Her left leg was cold, cyanotic and moderately swollen from groin to toes. No arterial pulses could be palpated below the inguinal region on the left side. The right leg and both upper extremities were unremarkable. The heart was moderately hypertrophied

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From the Department of Pathology, The Methodist Hospital and ownstate Medical Center, S.U.N.Y., Brooklyn, N.Y.

Because of the unique appearance, the heart of this case was subitted to the Armed Forces Institute of Pathology. They prepared oss photographs, sections and photomicrographs (AFIP 1556129).

and the lung was clear. The electrocardiogram showed atrial fibrillation. She immediately received heparin and methyl prednisolone intravenously. Left femoral arterial occlusion was suspected and she underwent femoral embolectomy. A few small blood clots were removed. Immediately after operation, peripheral arterial pulsation was slightly improved but the purplish skin discoloration persisted. On the second postoperative day, the entire left leg showed early gangrene. No pulses could be palpated. Subsequently, she became hypotensive and oliguric and died of cardiac arrest four days after operation.

At autopsy (A-75-120), the heart weighed 330 gms and the chambers were of usual size. The epicardium and myocardium were unremarkable. There was a pedunculated double-headed polypoid thrombus with a Y-shaped stalk attached to the atrial surface of the base of the posterior mitral leaflet near the posterior commissure (Fig. 1, 2). A small organized thrombus resembling a stalk without the club-shaped head was also seen on the atrial surface of the posterior leaflet near the anterior commissure. The anterior mitral leaflet and chordae tendineae were slightly thickened. The aortic cusps showed fibrous thickening but no adhesions of commissures. The tricuspid and pulmonic valves were unremarkable. Histologic sections showed a palisading granuloma of the mitral ring with fibrinoid necrosis, lymphocytic infiltration, a few multinucleated giant cells, proliferation of fibroblasts and neovascularization (Fig. 3). The stalk showed an organized thrombus with hyalinized fibrous tissue. The

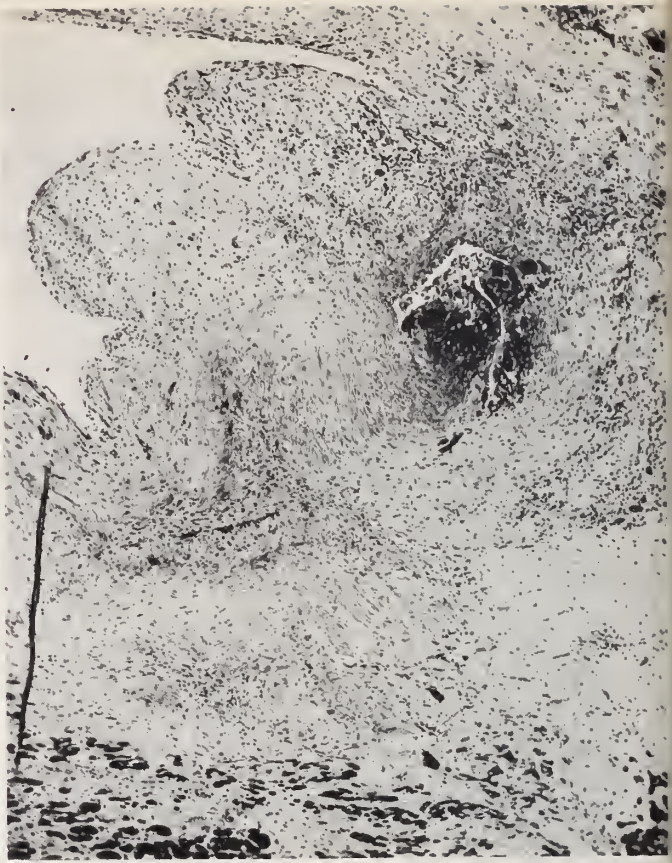

FIG. 2. Photomicrograph of granuloma in the mitral ring with a organizing fibrous stalk and polypoid thrombus. (H & E ×5)

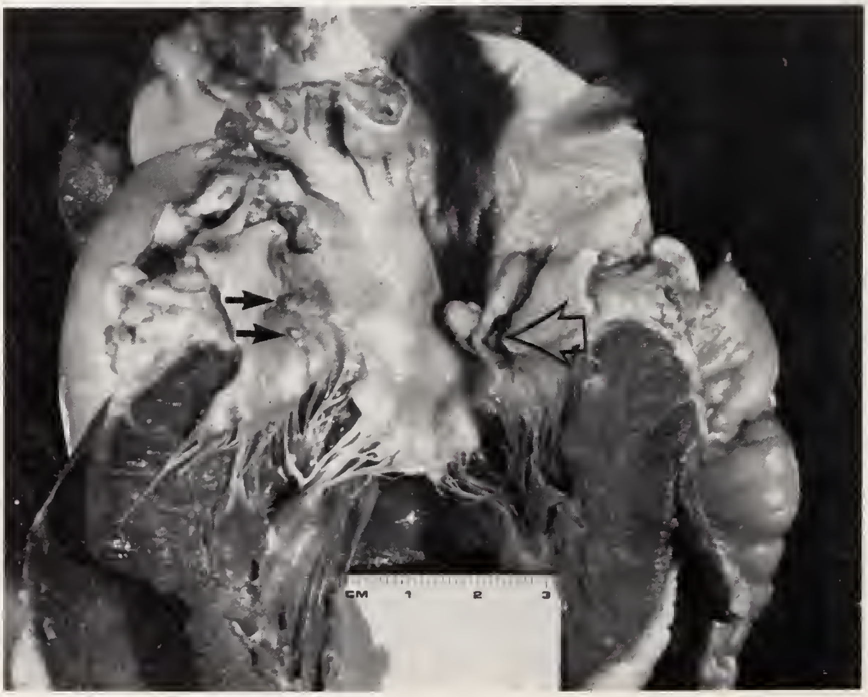

FIG. 1. A pedunculated double-headed thrombus with Y-shaped stalk attached to the base of the posterior mitral leaflet near the posterio commissure (hollow arrow) and two small vegetations resembling decapitated stalks on the other side (solid arrows).

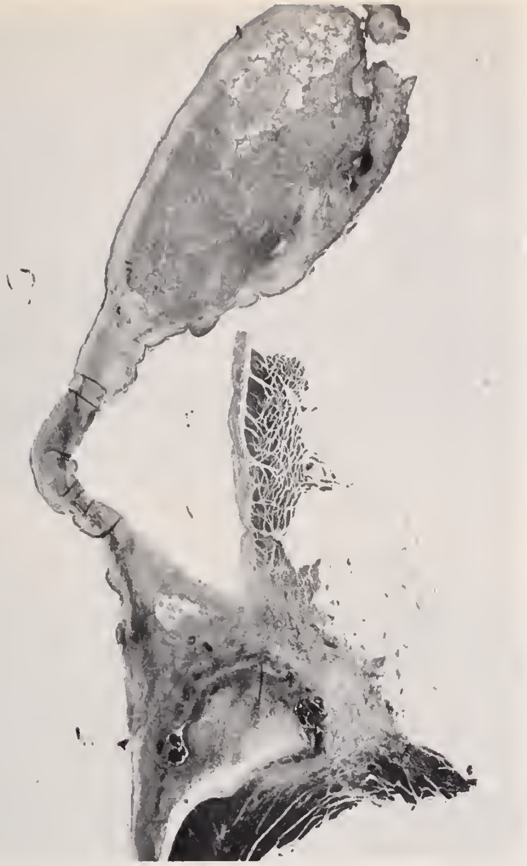

FIG. 3. Photomicrograph of mitral ring showing central fibrinoid necrosis and peripheral fibrosis with chronic inflammatory cell infiltration, palisading fibroblasts and a few giant cells. (H & E ×45)

double-headed thrombi were composed of blood clot, fibrinous material and clusters of foamy cells centrally and organizing fibrous tissue at the periphery. No bacteria or fungi could be demonstrated in the granuloma or thrombus. No mural thrombi were present in the aorta or the iliac arteries. The left lower extremity could not be dissected because of autopsy limitations. The other significant findings were severe deformities of fingers and toes, and bilateral massive pulmonary thromboembolism.

Discussion

Rheumatoid heart disease is defined as a pathognomonic palisading granuloma with fibrinoid necrosis involving the epicardium, myocardium, endocardium or valvular structure in patients with rheumatoid arthritis. It has been reported in three to five percent of hearts in autopsy studies of rheumatoid patients (2, 3).

The case reported herein showed several elongated slender thrombi of unique appearance arising from granulomatous involvement of the mitral ring. We postulate that some of these thrombi embolized to the left femoral artery resulting in gangrene of the leg. In a review of 53 reported autopsy cases of rheumatoid heart disease, the authors found four cases–two each in mitral and aortic valve (1, 4–6). Only one of these four cases showed an infarct in the spleen and kidney possibly due to embolization (4). The rare occurrence of mural thrombi in rheumatoid heart disease is explained by the preferential location of the granuloma in the fibrous core of the cusp and ring without extension to the endocardium (6). Although thrombus formation is rare in rheumatoid heart disease, the clinical significance of distant embolization to vital organs should be kept in mind.

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Stage D Squamous Cancer of the Bladder: Report of a Seven-Year Survival after Cystectomy

A. RANALD MACKENZIE, M.D., F.A.C.S. AND HAROLD Z. SCHEINMAN, M.D.

Squamous cancer of the bladder is characterized by invasiveness and rapid demise (1–3). Presently if prompt cystectomy is performed reasonable cure rates may be obtained for squamous cancer of the bladder as demonstrated in the following case.

Case Report

A 62-year-old white male developed hematuria in November 1971. On December 26, 1971, in another hospital, he underwent suprapubic excision of a deeply infiltrating squamous cancer of the bladder involving the right side of the bladder and trigone. When admitted to Long Beach Memorial Hospital on January 16, 1971, he was voiding every 20 minutes with hematuria and clots.

Examination was unremarkable except for mild hepatomegaly, a dry, healing suprapubic incision, and induration in the right paraprostatic area. Excretory urography disclosed greatly delayed function of the right kidney, marked hydroureter to the ureterovesical junction, and gross deformity of the bladder.

In view of his voiding frequency and poor prognosis, laparotomy was performed on January 19, 1972 with the intention of creating a urinary diversion and later giving palliative or precystectomy x-ray therapy. The bladder was cauterized by instillation of ten percent formalin. No metastatic nodes were found. Accordingly cystectomy was performed. The bladder was bulky, and indurated in its attachment to the anterior abdominal wall and to the right side of the pelvis. The bladder was removed without violating its interior. An ileal conduit was made.

Surgical Pathology

The specimen consisted of a urinary bladder and prostate. On opening the specimen, the lumen was filled with a large blood clot and some necrotic fragments of tumor. On the right posterior wall, there was an ulcerated, firm, nodular area which invaded the prostate on its superior surface. The ureters were dilated. The left was patent and the right obliterated. On section through the wall, the tumor extended through the bladder muscle and invaded the adipose tissue posteriorly (Fig. 1).

Examination of 100X magnification revealed a deeply infiltrating squamous cell carcinoma of the urinary bladder that extended into the prostatic bed. (Figs. 2, 3.) The tumor consisted of masses of epidermal cells, most of which were moderately well differentiated. There were intercellular bridges and individual cell keratinization present. There were also moderate cellular atypism with nuclear hyperchromatism and mitosis. A moderate chronic inflammatory response was also present in the tumor.

Following surgery the course was uneventful. To date he has received no x-ray therapy. He remains free of local recurrence or metastases seven years after cystectomy.

Discussion

The incidence of squamous cancer of the bladder varies in different series depending on their composition. In large series of bladder tumors that include the most favorable lesions, the incidence is one to three percent (3,4). In other series of bladder cancers selected by virtue of their therapeutic requirements, the incidence is over ten percent (5,6).

Invasion is almost invariably present at diagnosis with death within a year in two-thirds of cases (1,3,7,8). Survival beyond five years was quite exceptional until recently. Schwartz et al reported one survivor in 29 cystec-

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From the Section of Urology, Department of Surgery and the Department of Laboratories, Long Beach Memorial Hospital, Long Beach, N.Y. 11561.

Requests for reprints should be sent to Dr. A. R. Mackenzie, 20 West Park Avenue, Long Beach, N.Y. 11561.

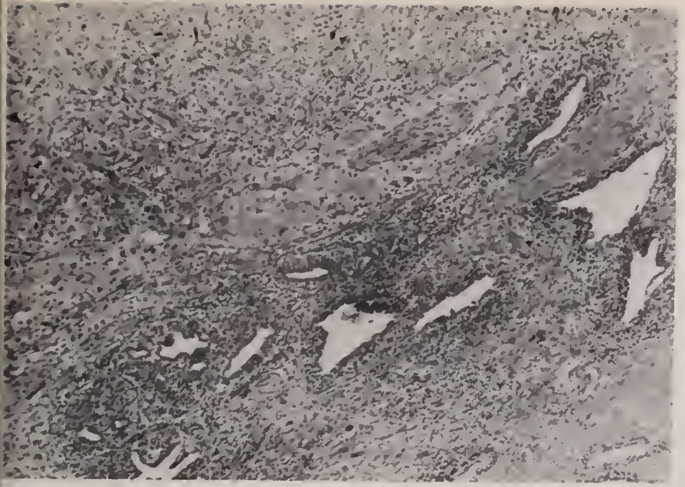

FIG. 1

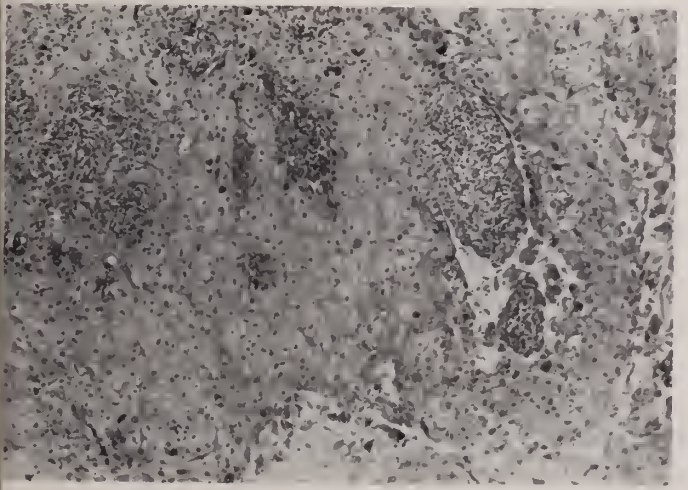

FIG. 2

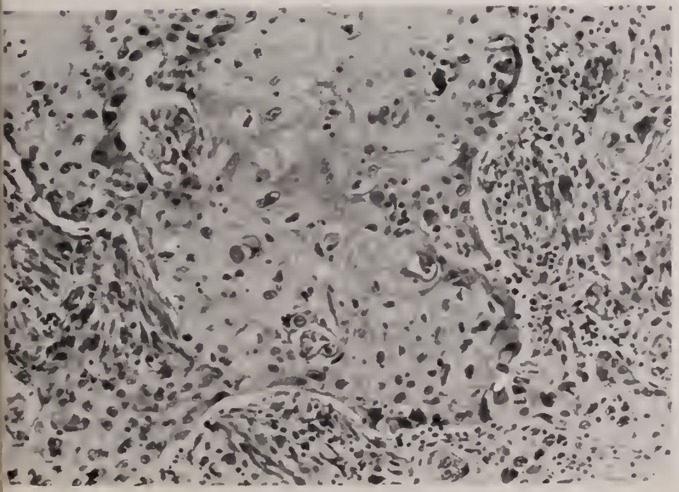

FIG. 3

tomies (5). Kovetz and Weinberg had one survivor in 14 patients but he too died of metastases in the sixth year (9). All 24 patients in the Bristol Bladder Tumor Registry succumbed to their disease (2).

Recent reports indicate a less dismal prognosis in patients treated by cystectomy with or without radiation. Bessette et al reported survival for periods from five to 11.5 years in five of 68 patients studied (3). Four had stage C tumors; two were treated by segmental resection, and the others by cystectomy and by anterior exenteration respectively. A fifth had a superficial lesion that was cured by transurethral resection and external radiation.

Richie et al report a five-year survival of 12 patients in a group of 28 treated by radical cystectomy with or without radiation (7). One patient with stage D cancer was alive five years afterwards. Johnson et al found 34 percent of patients with stage B_2 and C lesions alive five years after preoperative x-ray therapy and cystectomy (8). All 42 patients with stage D squamous cell cancer were dead within three years. Radiation alone has had little success (6,8).

Stage D cancer of the bladder is seldom cured. Whitmore and Marshall had two patients out of 55 with stage D_1 transitional cell cancer of the bladder alive five years after radical cystectomy (10). Included in this group were 20 patients with invasion of the prostate; nine had no demonstrable metastasis. None of those 20 patients was a five-year survivor.

The patient reported herein is free of disease seven years after cystectomy for squamous cancer which penetrated the perivesical fat and invaded the stroma of the prostate.

Summary

A 62-year-old man was explored for palliative treatment of advanced squamous cancer of the bladder. Absence of metastatic disease led to cystectomy and ileal conduit diversion. He received no x-ray therapy before or subsequent to operation and has remained free of disease for seven years. Surgical extirpation appears to be the most successful method of dealing with squamous cancer of the bladder.

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Sympathetic Pupillary Activity in Jewish Ethnic Groups

NETANEL LAOR, M.D. AND AMOS D. KORCZYN, M.D., M.Sc.*

Abstract

Pupillary responses in five Jewish ethnic groups to phenylephrine and to hydroxyamphetamine were studied. No significant differences were demonstrated, and it is concluded that there is no difference in adrenergic receptor sensitivity or in presynaptic reservoirs in the ocular sympathetic system among these ethnic groups.

Introduction

Chen and Poth presented evidence that the mydriatic activity of sympathomimetic drugs differs among races (1, 2). The various ethnic groups of the Jewish people differ in facial and corporeal features, amount of pigmentation and in the frequency of some inherited diseases (3, 4). We wanted to find out whether Jewish ethnic groups also differ in their pharmacologic responses to these agents.

Materials and Methods

Sixty-nine volunteers aged 15–30 (mean, 21) years participated in this investigation. Subjects were healthy nonsmokers. All had brown pigmented irides. The ethnic origin of the subjects was as follows: 14 Ashkenazi, 17 Sephardic, 20 Yemenites, 10 Iranian and 8 were from Kuchin, India.

The pupillary responses were measured according to a standard procedure (5, 6). All observations were made during the morning hours. The subjects were fixating at a distance with a constant room luminosity of approximately 200 Lx. Apparent pupillary size was estimated through direct comparison with a series of circles with diameters of 2.0, 2.5, 3.0 . . ., 9.0 mm. With this method, a trained observer can easily reach an accuracy of ±0.5 mm.

The drugs used were phenylephrine, 5%, and hydroxyamphetamine, 0.5%, given as eye-drops, 0.05 ml into one conjunctival sac. Measurement of pupillary size was performed repeatedly for one hour or more, and the maximal change was recorded.

The responses of the pupil were calculated as the ratio:

$$\text{M.R. (mydriatic ratio)} = \frac{\text{maximal diameter after mydriatics}}{\text{pupillary diameter before mydriatics}}$$

Statistical analysis consisted of Student t-test.

Results

The mean pupillary size was similar in the five ethnic groups tested. No significant difference was observed in the diameter of the pupils either at rest or following application of drugs. The M.R.'s for either drug were also similar in the various groups (Table I).

Discussion

Racial differences in the responses to mydriatics were demonstrated by Chen and Poth, but this topic was not followed up (1, 2). However, there is evidence for genetic control of pupillary responses to these agents (7, 8), and patients with Down's syndrome react with particularly strong mydriasis (9).

We observed quantitatively similar responses of the various ethnic groups tested, both to the direct-acting adrenergic receptor stimulant phenylephrine, and to hydroxyamphetamine, which acts through release of endogenous norepinephrine (10). Thus, we concluded that the ocular sympathetic system is equal in its activity in the five ethnic groups examined, as is the smooth muscle reactivity to adrenergic stimulation. It is not clear that previous studies were controlled for iris color, as was the

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* From the Department of Physiology and Pharmacology, Sackler School of Medicine, and Department of Neurology, Beilinson Medical Center, Tel-Aviv University, Ramat Aviv, Israel.

Requests for reprints should be sent to Dr. A. Korczyn, Department of Physiology and Pharmacology, Tel Aviv University Medical School, Ramat Aviv, Israel.

TABLE I

Pupillary Diameters (mm, Mean ± SD) Before and After Mydriatics, and the Mydriatic Ratios (Mean ± SD)

Ethnic Group	Number of Subjects	Resting Diameter	Hydroxyamphetamine		Phenylephrine	
			Diameter	Mydriatic Ratio	Diameter	Mydriatic Ratio
Ashkenazi	14	4.9 ± 1.0	6.7 ± 0.8	1.4 ± 0.2	7.6 ± 1.0	1.6 ± 0.2
Sephardic	17	5.2 ± 0.9	7.0 ± 0.2	1.4 ± 0.4	7.6 ± 0.7	1.5 ± 0.4
Kuchinic	8	5.4 ± 0.6	6.9 ± 0.7	1.3 ± 0.3	7.8 ± 0.5	1.5 ± 0.3
Persian	10	4.7 ± 0.4	6.4 ± 0.5	1.3 ± 0.2	7.3 ± 0.8	1.6 ± 0.4
Yemenite	20	5.1 ± 0.4	6.8 ± 0.4	1.3 ± 0.1	7.8 ± 0.5	1.5 ± 0.2

present work. Melanin is known to bind various drugs in a nonspecific manner (11, 12), and this may be responsible for the ethnic differences previously reported.

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Selective Arterial Embolization for Hemorrhage Following Hip Fracture Fixation

JEFFREY MUHLRAD, M.D.

At City Hospital Center at Elmherst, we attempt to treat intracapsular fractures of the hip in younger patients by closed reduction and open pinning with a sliding nail plate (Howmet). If the reduction can be accomplished, a free-sliding nail is inserted. This sliding nail permits some fracture collapse and permits progressive fracture impaction. It can be securely attached to a variable angle femoral side plate, similar to a McLaughlin plate. The variable angle plate allows individualized fixation of all angles of femoral neck inclination and anteversion.

The following is a case report of massive postoperative bleeding, the cause of which was obscure but proved to be secondary to a laceration of a perforating branch of the profunda femoris artery at the time of sliding nail insertion, and the use of gelfoam embolization to obtain hemostasis during and following femoral angiography.

Case Report

The patient was a 61-year-old retired longshoreman admitted to Elmhurst General Hospital on May 28, 1977 with an intracapsular hip fracture. He was a known chronic alcoholic and smoker. Past medical history was negative for ulcer disease, hepatitis or bleeding diathesis. Review of systems was noncontributory. On physical examination, the skin was without jaundice or ecchymosis. The head was homocephalic. There was no jugular venous distention, lymphadenopathy or thyromegaly. The lungs were clear except for scattered rhonchi at the left base. Heart sounds were well heard with midsystolic murmur. The abdomen was protuberant, no shifting dullness or collateral veins, with the liver edge two finger breadths below the right costal margin. The right lower limb was shortened and externally rotated. Neurologic examination showed bilateral resting tremors. The remainder of the examination was within normal limits.

X-ray showed a fully displaced (Garden IV) in tracapsular fracture of the right hip. Laboratory data on admission revealed complete blood count and serum electrolytes within normal limits. SMA_{12} showed an elevated bilibrubin 2 mg %–9 mg % alkaline phosphatase 192 $m\mu$/ml, serum glutamic oxalic transaminase 117 $m\mu$/ml, lactic dehydrogenase 486 $m\mu$/ml, phosphorous 2.6 mg %, calcium 7.5 mg %, total protein 5.9 g %, albumin 2.3 g %. Prothrombin time was 12.6 sec/11.8 control and platelets were normal.

Hospital Course

On May 31 he underwent surgery under general anesthesia with x-ray control. At the time of the procedure, there was an estimated 400 cc of blood loss and this was primarily coming from the posteromedial aspect of the incision. This was much more than usual for nail plating in intracapsular fracture with a steady ooze rather than spurts. After achieving adequate hemostasis, the wound was closed in the usual fashion. A satisfactory placement of the nail and reduction and impaction of the fracture were obtained. Initially, he did well; but by the second postoperative week the proximal thigh was grossly and massively swollen. Infection, deep thrombophlebitis and/or deep hematoma were suspected. Approximately 200 cc of serosanguinous fluid was aspirated.

The culture grew enterococcus and aerobacter aerogenes. On June 28, 1977, the distal margin of the wound was opened and betadine packing placed for drainage. Intravenous antibiotics oxacillin and gentamycin were administered. Drainage was grossly bloody and bright

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From the Department of Orthopaedics, Mount Sinai School of Medicine of The City University of New York, New York, N.Y. 10029.

Requests for reprints should be sent to Dr. Jeffery Muhlrad, Orthopaedics Department, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, N.Y. 10029.

red like arterial blood but without pulsations. From June 1 until July 12 his hematocrit was stable at 29%. On July 12 he suddenly began to bleed profusely from the wound. The hematocrit dropped to 19%. Because this was progressive and uncontrolled despite multiple transfusions, the wound was explored. In the operating room under general anesthesia, the original incision was opened. Several small veins and arteries were ligated and the wound packed open.

He received six units of whole blood and two units of fresh frozen plasma. Postoperatively he was transferred to the surgical intensive care unit where hematologic workup revealed prothrombin time 13.3/11.3 control, partial thromboplastin time 46.8/41.1, and thrombin time 25/18.1 (slightly prolonged). Fibrinogen 286 mg bleeding time by ear lobe puncture was three minutes, peripheral smear showed adequate platelet count. These findings were consistent with his liver abnormality and so he was treated with aquamephyton (Vitamin K).

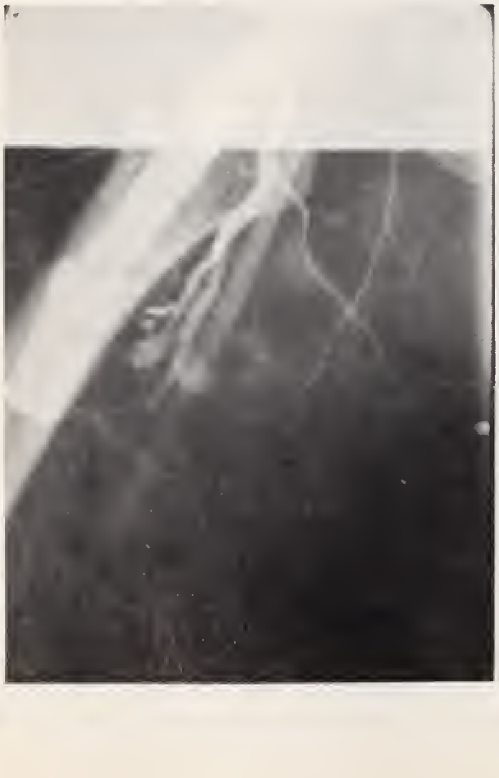
Despite all of these measures, his bleeding actively continued thus requiring another six units of whole blood over the next twenty-four hours. On July 13 because of suspicion of major arterial bleeding, a right femoral angiogram was performed using the Seldinger technique. Two sites of bleeding with extravasation of dye were demonstrated involving the proximal right profunda femoral artery at the level of the proximal part of the McLaughlin side plate (Fig. 1). Since these were the apparent sites of bleeding, the vessels were selectively embolized with pledgets of gelfoam sponge (Dr. Sprayregeu) (2–4 mm pieces mixed with contrast material). This was successful in arresting the blood loss and no further transfusions were required. After a two-week period the angiographic study was repeated (Fig. 2). There was no further extravasation of contrast material. The wound has subsequently healed by granulation though it drained for some weeks. Thus far, no evidence of deep infection endangering the plate, nail or joint has appeared. The patient is receiving physical therapy in ambulation.

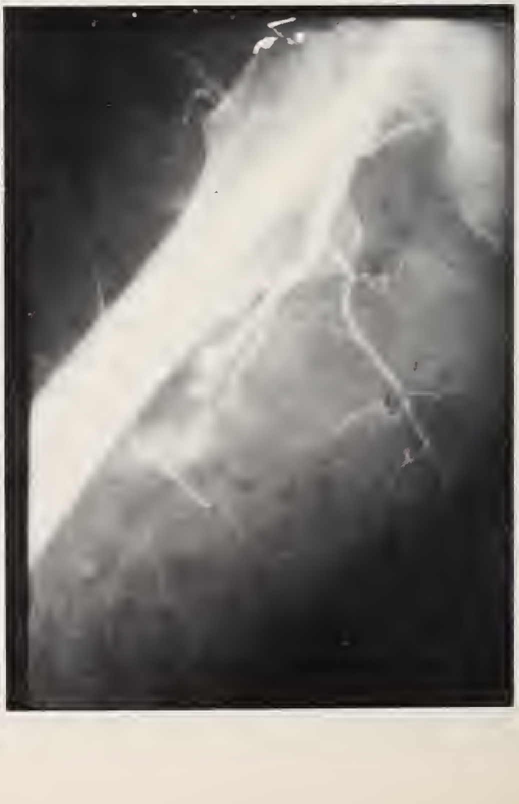
Discussion

There are a number of reports of cases in which there was an injury to the femoral vessels during or soon after operative fixation of fractures of the hip (3, 6). Laceration of the vessels by sharp fragments of bone may occur during the fracture or while transporting the patient to or in a hospital. The same mechanism of injury has even been reported to occur weeks after fixation of the fragments (9).

Arterial penetration by a screw and false aneurysm of the profunda femoris artery secondary to arterial penetration by a drill bit are unusual examples of the mechanisms of late vascular injury (1, 4). We are reporting a case in which a similar mechanism producing injury to a perforating branch of the profunda femoris artery was managed by selective arterial embolization with gelfoam.

Angiographic diagnosis and treatment of bleeding by selective embolization was utilized by Margolies et al in





the management of pelvic fracture hemorrhages (8). This is an extremely useful application since identification of the bleeding site by surgical exploration is exceedingly difficult. Many others have employed this technique successfully under similar clinical circumstances (2, 7). Recently, Halpern reported a case in which massive bleeding occurred two weeks postoperatively an Austin-Moore arthroplasty. In this case, angiography using the Seldinger technique demonstrated bleeding in the inferior gluteal artery which was then selectively embolized with gelfoam pellets.

It is apparent from this case that laceration of the deep branch or branches of the profunda femoris artery is a real hazard in open reduction and internal fixation of hip fractures, if careful technique is not observed.

The profunda femoris artery at first lies lateral to the femoral artery; it then runs posterior to it and the femoral vein, to the medial side of the femur, passing distally posterior to the adductor longus muscle. The medial femoral circumflex artery arises from the medial aspect of the profunda, and winds around the medial side of the femur, passing first between the pectineus and psoas major and then between the obturator externus and the adductor brevis. The perforating arteries, usuallly three in number, perforate the adductor magnus to reach the back of the thigh. They pass posteriorly close to the linea aspera of the femur under cover of small tendinous arches in the muscle. To avoid injury to these close lying vessels, the skin incision and surgical approach should be kept lateral not posterior. When securing the side plate to the proximal femur, Bennett retractors are placed about the medial aspect of the shaft when drilling, tapping and using the depth gauge to protect the soft tissues and blood vessels from injury by over penetration. Screws of the correct length must be inserted.

If an accident should occur and suspicion of persistent arterial bleeding become prevalent, early angiography and selective embolization with gelfoam pledgets is extremely worthwhile.

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Vitamin Supplements and Malnutrition in a Hospital Medical Population

JOSEPH DUVA, M.D.* and CHARLES D. GERSON, M.D.

Abstract

A group of medical patients was surveyed to determine the percent that were taking vitamins to supplement their diets. Thirty-eight percent of the subjects were ingesting vitamin supplements. There was no significant relationship between vitamin intake and several parameters of malnutrition, disease category or obvious dietary deprivation of fruits and vegetables. A subgroup of subjects advised by their physicians to take vitamins appeared to be even less malnourished than those taking vitamins voluntarily.

Introduction

Hypovitaminosis has been documented in hospitalized medical patients (1, 2). In one study by Bollet et al (2), only 6% of the subjects were taking vitamin supplements. Vitamin therapy has caught the fancy of the public and we have recently noted a much higher incidence of vitamin ingestion in a hospitalized population. These facts prompted us to study the frequency of vitamin ingestion in general medical patients in our hospital. This information was related to several parameters of malnutrition (3, 4), as well as to dietary factors and disease category in each subject. We also determined whether vitamin therapy was selfinitiated or recommended by a physician.

Materials and Methods

Age, sex, diagnosis and weight change in the past six months were recorded for each patient. Diet was evaluated with a selected focus. Subjects were queried by recall whether they were on medically recommended restrictive diets and how much fruit, vegetables and fruit juice they consumed during an average week. Ingestion of fruits and vegetables was considered low if intake was two or less times per week and adequate if two or more times per day. Patients were queried regarding vitamin pill intake. Brand, frequency, and duration were recorded. Mid-way through the study, it was noted whether the patient's physician had recommended vitamin therapy or whether it was voluntary on the part of the patient.

Height was measured using a hospital scale, in most patients. When this was not possible, stated height was used. Weight was measured using a hospital scale in all patients. Triceps skin fold thickness was measured in duplicate with Lange calipers (5) using standard method at the left mid-arm. Serum albumin was measured by automated Biuret method in all subjects.

Weight for height was compared to a standard reference for normals (6). Weight was considered low if more than ten percent below normal (3). Triceps skin fold thickness was compared to the values obtained for a normal population in the Ten State Nutrition Survey (7). Values below the fifteenth percentile were considered low. Serum albumin below 3.5 gm per 100 ml was considered low.

Subjects. Two hundred thirteen patients were interviewed. Two patients were eliminated from the study because of inability to acquire all the information. One hundred sixty-nine were inpatients and forty-two were outpatients. There were 78 males and 133 females in the study. Disease categories were represented as follows: 32% cardiovascular, 25% gastrointestinal, 17% neoplasia and 27% other.

Results

Thirty-eight percent of the study population were taking vitamins, 40% among females and 35% among males. Since the percent was almost identical in inpatients and outpatients, 38% versus 36%, the data for both categories was pooled. During the second half of the study, 38 subjects who were taking vitamins were asked whether

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From the Department of Medicine, Mount Sinai School of Medicine of The City University of New York, New York, N.Y. 10029.

* This study was executed during a third-year medical school elective.

Requests for reprints should be sent to: Charles D. Gerson, M.D., Mount Sinai School of Medicine, One Gustave Levy Place, New York, N.Y. 10029.

they were doing so at the advise of their physician. Sixty-six percent of the 38 subjects were ingesting vitamins voluntarily, with only 34% because it had been recommended.

Protein calorie malnutrition was assessed by serum albumin, weight for height and triceps skin fold. Subjects with malnutrition according to these parameters did not have significantly greater intake of vitamin supplements (Table I). Thus, while 38% of all subjects ingested vitamin and 41.7% had one or more abnormal nutritional measures, malnutrition did not appear to influence vitamin intake. It is of interest that those patients advised by their physicians to take vitamins were less likely to have abnormal nutritional measures than the voluntary group (Table II).

When the study population was divided by disease category, there was no significant difference in vitamin ingestion although the figure for the neoplasia group, 51%, was slightly higher than the rest (Table III). Malnutrition did appear to be more prevalent in neoplasia patients, especially as measured by serum albumin which was low in 44% as compared to 15% for the rest ($X^2 = 4.18$, $p < 0.05$).

Dietary history was focused on fruit and vegetable intake because vitamin C and all of the B vitamins are derived from them. This aspect of diet did not appear to influence the ingestion of vitamin supplements. Forty-one percent of those with low fruit and vegetable intake were taking vitamins and 28% of subjects who rarely drank fruit juice ingested vitamins. This is in comparison to 48% of those with adequate fruit and vegetable intake and 40% of subjects who drank fruit juice daily. It is of interest that low fruit and vegetable ingestion was significantly more common in the gastrointestinal group, 37%, than in all the others, 13% ($X^2 = 8.23$, $p < 0.005$).

While age was not a statistically significant factor, a slightly higher percent of subjects over sixty, 44%, took vitamin compared to 35% for the others.

TABLE I

Percent of Subjects Taking Vitamins with Low and Normal Albumin, Skin Fold, and Weight for Height

	Albumin		Triceps Skin-Fold		Weight for Height	
	% taking vitamins	% total	% taking vitamins	% total	% taking vitamins	% total
Low	33	24	44	26	55	19
Normal	43	76	37	74	34	81

TABLE II

Percent of Low Nutritional Measures among Subjects Taking Vitamins Voluntarily or According to Physician's Advice

	Low Triceps Skin Fold	Low Weight	Low Albumin
Voluntary	31%	40%	19%
Physician	13%	15%	14%

TABLE III

Percent Taking Vitamins and Percent with Malnutrition Parameters According to Clinical Groups

	Neoplastic	Gastro-intestinal	Cardio-vascular	Other
Vitamins	51%	38%	36%	32%
Low albumin	44%	17%	12%	26%
Low weight	26%	19%	16%	18%
Low skin fold	41%	27%	22%	23%

Discussion

The aim of this study was to ascertain the percent of medical patients in a hospital who were taking supplementary vitamins and to determine whether the patients taking vitamins differed from those who were not according to nutritional parameters, disease category or diet. We found that 38% of subjects were taking vitamin preparations. While 41.7% of subjects had one or more abnormal values for the nutritional measures of serum albumin, triceps skin fold or weight for height, this group was not more likely to be ingesting vitamins than subjects with normal nutritional values. A minority of patients taking vitamins had been advised to do so by their physician. The group that had been so advised appeared to be less malnourished than the other patients who ingested vitamins. Thus, evidence for malnutrition did not have any significant relationship to supplementary vitamin intake.

While we did not establish a direct correlation between vitamin deficiency and protein calorie malnutrition in this study, several published reports have shown the frequency of multiple vitamin deficiency in patients with malnutrition (1, 2, 8). Both measures are probably related to decreased food intake as well as the catabolic effect of illness. We have previously observed folic acid (9) and ascorbic acid deficiency (10) in patients with protein malnutrition and inflammatory bowel disease.

Also, dietary intake of fruits and vegetables did not appear to influence supplemental vitamin ingestion. We observed that the patients who drank fruit juice daily were more likely to be taking vitamins than those who drank fruit juice rarely. This illustrates the lack of awareness of possible dietary deprivation. This was evident in the gastrointestinal group that was most likely to have a low fruit and vegetable intake because of their medical problem. This did not result in higher vitamin supplementation. Disease category did not significantly influence our results though it is noteworthy that the neoplasia group, with the highest percent of protein calorie malnutrition, did have more vitamin supplementation (51%) than the other groups.

Age did not appear to influence ingestion of vitamins. The geriatric population probably has greater need for vitamin support than any other adult age group. There have been numerous reports documenting vitamin deficiencies and poor oral intake of vitamins in the elderly (11, 12). We evaluated our data by decade and found no significant increase in vitamin supplementation with age though the percent among subjects over sixty (44%) was slightly higher than the percent for younger subjects.

Our results indicate that vitamin pill ingestion is common in a hospital medical population. Since we could not relate vitamin usage to nutritional status, disease category or dietary factors, it would appear that further study is needed to establish a more rational approach for recommending which patients need vitamin supplementation.

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Ophthalmologic Notes

KEITH M. ZINN, EDITOR

Bilateral Complete Colobomas with a Unilateral Optic Pit and Recurrent Retinal Detachment: A Case Report

KEITH M. ZINN, M.D.

Incomplete closure of the fetal fissure of the globe during intrauterine development results in a coloboma (1). Incomplete colobomas can be divided into anterior and posterior defects. Anterior colobomas can involve the iris and/or the ciliary body whereas the posterior colobomas may involve the choroid retina, optic nerve or macula. Complete colobomas are a combination of anterior and posterior colobomas extending from the pupillary margin posteriorly to include the optic nerve. Colobomas are further divided along anatomical lines according to their location within the eye. Typical colobomas are located in the inferonasal quadrant while atypical colobomas are those defects outside the inferonasal quadrant.

A posterior coloboma affecting the optic nerve is often associated with poor vision in the eye along with nystagmus and strabismus. The eye may also be microphthalmic and the retinal detachments that occur in this clinical setting are extremely difficult to treat (2, 3). Colobomas are inherited as regular autosomal dominant traits (4).

An optic pit is a small circular depression measuring from ⅛ to ½ of a disc diameter in size. Optic pits are usually unilateral and located in the inferotemporal quadrant of the optic nerve head. Approximately 33% of the cases are associated with macular disorders (5, 6), for example, neurosensory macular detachment. Usually this is a localized lesion, but on occasion it may appear as a bullous retinal detachment (7). The optic pit consists of an outpouching of neuroectodermal tissue surrounded by a connective tissue capsule that traverses posteriorly through a defect in the lamina cribrosa and protrudes into the subarachnoid space. The genesis of optic pits is probably via an anomalous development of the primordial optic nerve papilla coupled with the failure of complete resolution of the neuroectodermal folds in the peripapillary region (8).

On rare occasions, complete colobomas may have an optic pit present. The latter condition may lead to a serous neurosensory retinal detachment. The combination of defects usually presents a complex management problem for the ophthalmic surgeon. The following case illustrates an approach to the possible clinical management of this disorder.

Case Report

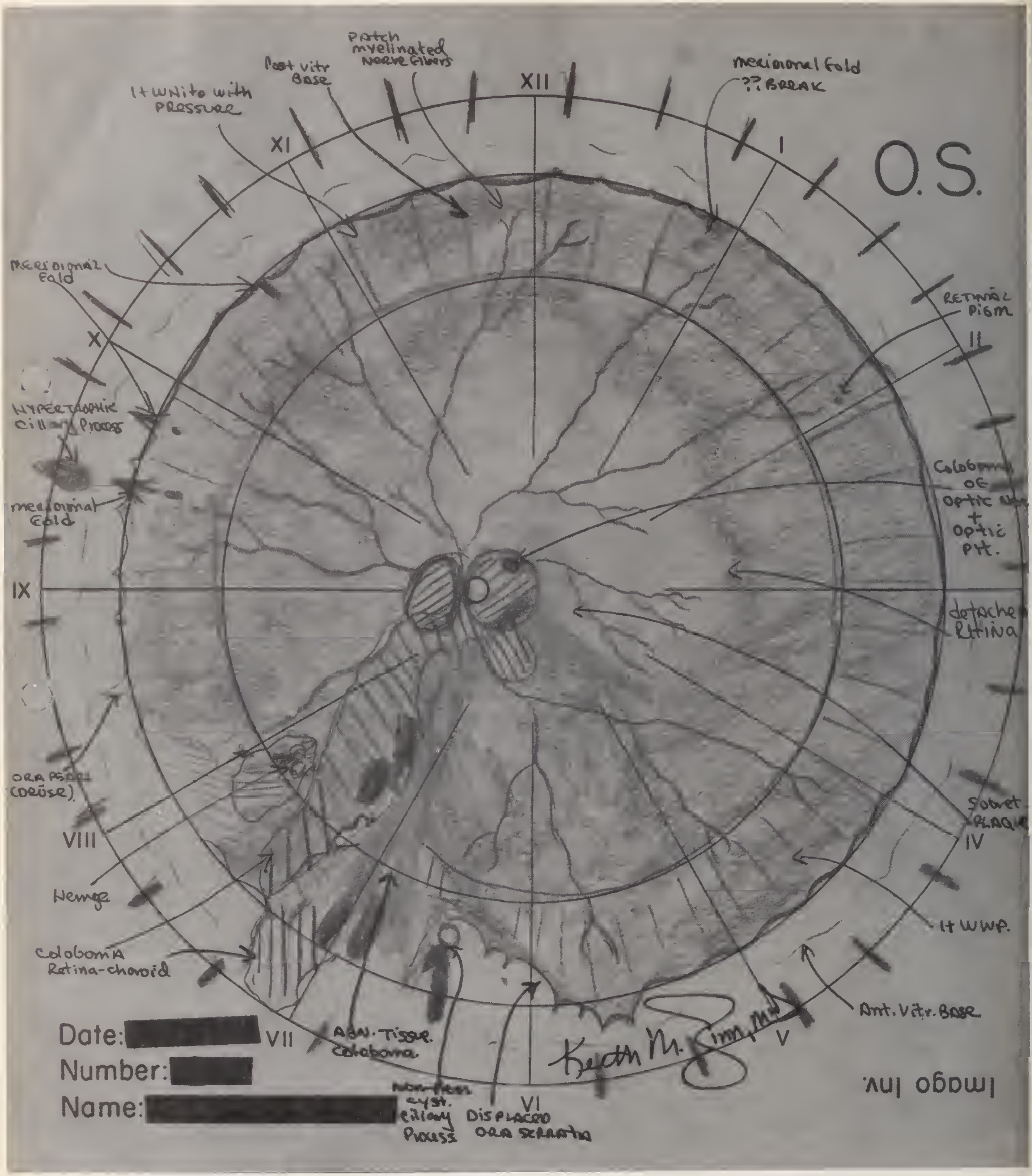
A 39-year-old Caucasian housekeeper who had been in essentially good health for many years had decreasing vision in the left eye of at least ten days' duration. Visual acuity, with correction, was 20/60 in the right eye with a +0.50 diopter sphere+3.50 diopter cylinder axis of 100° and hand motion at ½ foot in the left eye with a +0.75 diopter sphere+3.00 diopter cylinder axis of 95°. Manifest refraction could not improve the visual acuity in either eye.

Extraocular motility studies revealed a full range of motion of either globe in all standard fields of gaze and there was nystagmus in the horizontal meridia. The eyes appeared to be grossly straight in the primary position of gaze as well as in all other cardinal fields of gaze.

Cranial nerve function II, III, IV, V (ophthalmic division), VI and VII were grossly intact bilaterally except for extreme reduction in the visual field on the left side. Because of the severe nystagmus, formal visual fields could not be adequately performed.

The lids, ocular adnexae and lacrimal gland apparatus,

From the Department of Ophthalmology, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.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IX
detache Retina
ORA PEARL (DRÜSE)
Subret. PLAQ
VIII
IV
Hemge
lt WWP.
Coloboma Retina-choroid
Ant. Vitr. Base
VII
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V
Keith M. Zinn, MD
Non-Pigm cyst. ciliary Process
VI
DISPLACED ORA SERRATA
Imago Inv.

Date: [redacted]
Number: [redacted]
Name: [redacted]

FIG. 1. A fundus drawing of the patient's left eye showing the typical coloboma involving the ciliary body, pars plana, choroid, retina and optic nerve head in the inferonasal quadrant. Note the optic pit and neurosensory retinal detachment. Subretinal glistening yellow particles were also noted in the area of the retinal detachment. The etiology of these particles is unknown.

conjunctivae, corneae and sclerae were grossly within normal limits bilaterally, although the globes did appear to be slightly microphthalmic bilaterally.

The intraocular pressures were 23 mm of mercury in the right eye and 6 mm of mercury in the left eye by applanation tonometry.

Slit lamp examination of the anterior chambers revealed them to be clear, of moderate depth with Grade III open anterior chamber angles bilaterally. Several scattered iris nevi were present that were flat with well circumscribed borders and were perfectly benign in their appearance. The irides were green bilaterally and pupillary reactions on the right appeared to be within normal limits, but a Marcus-Gunn pupil was present in the left eye. The left pupil did react well to accommodative effort.

The lenses had cataract changes that consisted of anterior and posterior cortical spoke-like opacities in the inferonasal quadrants bilaterally. There was a straightening of the normal peripheral lens curvature due to ciliary body colobomas with secondary loss of zonular connections in the inferonasal quadrants bilaterally. The vitreous cavities were grossly clear with evidence of posterior cortical vitreous detachments bilaterally.

Funduscopic examination revealed bilateral typical colobomas in the inferonasal quadrant extending from the pars plana region posteriorly to the optic nerve head region (Fig. 1). The optic nerve heads had a marked tilted appearance to them with deep colobomas on the nasal and temporal borders of each optic nerve head. The left optic nerve head had a congenital pit at about the 2:00 o'clock meridian with some retinal tissue overlying the pit region (Fig. 2). The right macula had a good foveal reflex with normal macula pigmentation. The left macula had a neurosensory detachment which extended out to the equator (Fig. 1). Peripheral indirect ophthalmoscopy did not reveal any retinal breaks or tears in either eye. However, there was an enlarged ciliary body process at the 6:30 o'clock meridian in the right eye along with a pars plana cyst.

Fluorescein angiography was performed in the left eye and did not reveal any leakage from the optic pit or optic nerve coloboma (Fig. 3).

Because of the poor dilating quality of the irides and the nystagmus, the patient had an examination under anesthesia performed at The Mount Sinai Medical Center and no evidence of a peripheral retinal break or tear was noted. Therefore, the patient was treated with argon laser photocoagulation therapy in the peripapillary region in an effort to create a scar or barrier between the optic pit and the subretinal space. The patient was placed on strict bed rest and over the next week the retina flattened out. The retina remained reattached for the next ten months with a visual recovery up to the 20/100 level OS. At this point a bullous redetachment of the retina occurred in the left eye. The patient was rehospitalized and had argon laser photocoagulation to the peripapillary region once again that was followed twelve hours later by scleral buckling surgery (360° external silicone buckle with 360° cryopexy treatment at the equator) and drainage of subretinal fluid followed by an intravitreal air injection. This resulted in reattachment of the retina. During the first four postoperative days, the patient was placed with the head in the prone position to facilitate the vitreous air bubble pressing against the optic nerve head and posterior polar region of the eye. The patient was subsequently discharged five days after

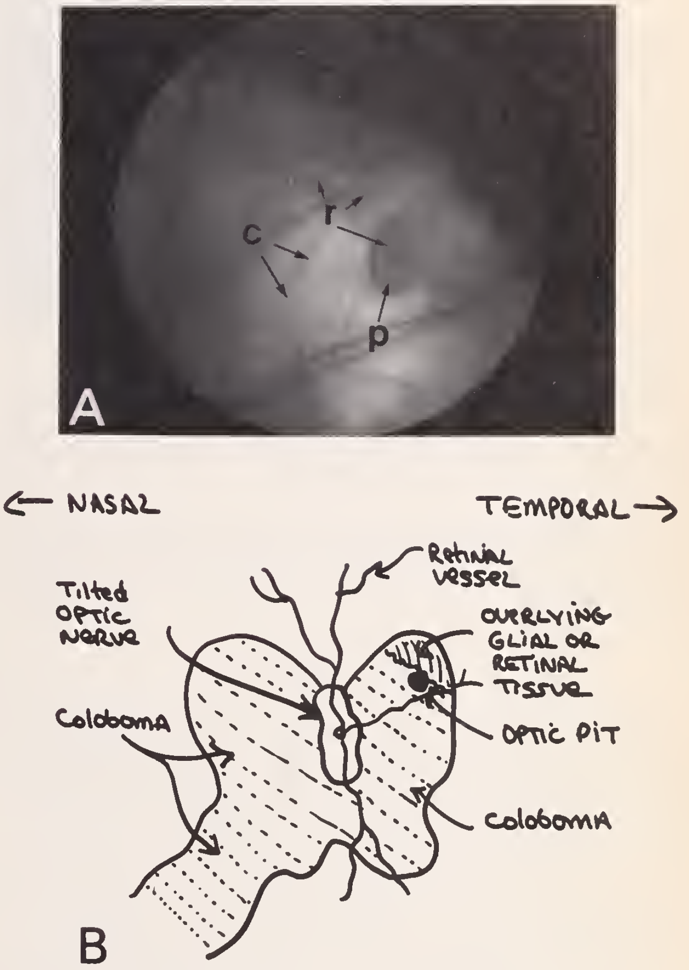
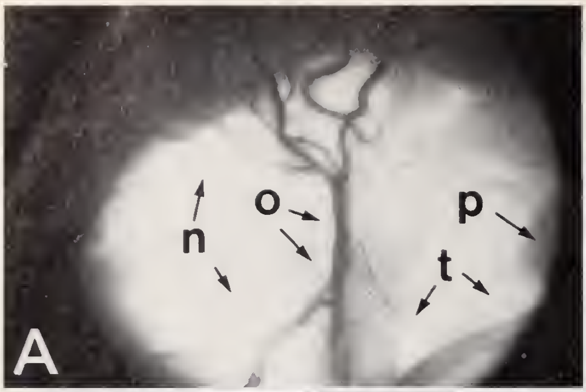
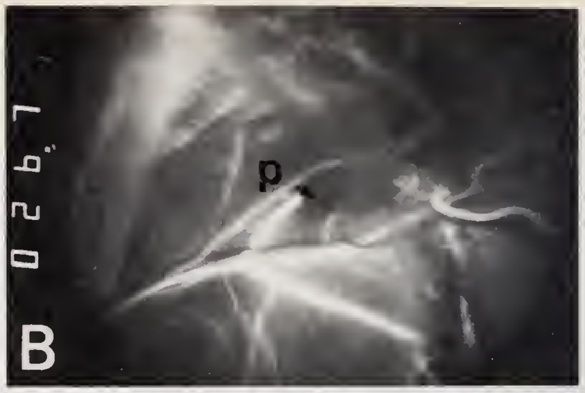
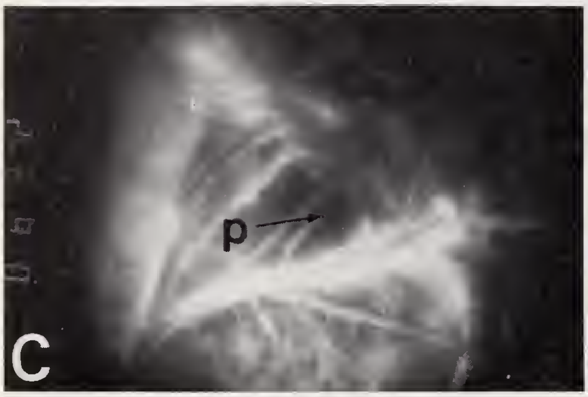


FIG. 2a. Fundus photograph superotemporal to the optic nerve head in the left eye. There is a colobomatous depression (c) immediately temporal to the optic nerve head. An optic pit (p) is present at the superotemporal border of the temporal coloboma. Glial or neurosensory retinal tissue (r) appears to be overhanging the superotemporal edge of the coloboma.

Fig. 2b. Schematic drawing of optic nerve head region in the left eye. Note overhang of glial or neurosensory retinal tissue at the superotemporal border of the temporal coloboma. There is an optic pit subjacent to this tissue in the superotemporal region of the coloboma.







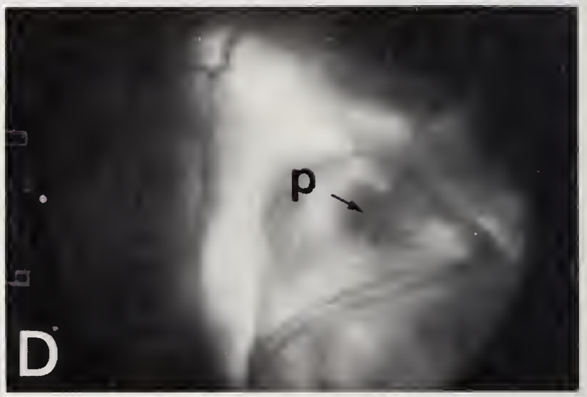


FIG. 3a. Red-free photograph of optic nerve head (o) with nasal (n) and temporal (t) coloboma. There is an optic pit (p). The optic nerve head is markedly tilted.

FIG. 3b. Early phase of fluorescein angiogram of same region as (a). No leakage of dye from optic pit (p).

FIG. 3c. Mid-phase of fluorescein angiogram—no leakage of dye from the optic pit (p).

26 FIG. 3d. Late phase of fluorescein angiogram—no leakage of dye from optic pit (p).

surgery and the retina has remained reattached for eighteen months. The postoperative visual acuity was 20/200 in the left eye.

Discussion

The association of optic pits and serous detachments of the macula are well known (5–7, 9). Although there have been several reports in the literature of unilateral and bilateral optic nerve colobomas (10–13), little attention has been focused on the association of optic colobomas with congenital optic pits and recurrent retinal detachments (4, 14). Savell and Cook (4) studied 25 members of a family in which 60% had atypical bilateral optic nerve colobomas. It was noted that 18% of these eyes had associated optic pits and of those eyes 50% had an associated retinal detachment involving the macula. Only one eye in their series had an extensive bullous retinal detachment. However, Savell and Cook's study (4) involved a family with atypical optic nerve colobomas. They also found that 66% of their patients with atypical colobomas had associated retinal detachments. No substantial figures are available in the literature with regard to the incidence of typical optic nerve head colobomas and associated congenital optic pits. No heterochromia iridis was noted in our patient, as reported by Drews (15).

In this case, our patient had complete bilateral typical colobomas including each optic nerve head. In the left eye, there was an associated congenital pit and recurrent nonrhegmatogenous retinal detachment. Goldberg (14) reported a similar case of an optic pit and an associated atypical optic nerve coloboma with serous retinal detachment. In his case, patching and mannitol had no effect on the subretinal fluid, but over a three-week period there was a spontaneous resorption of subretinal fluid. Jesberg and Schepens (3) reported poor results in the treatment of retinal detachments associated with choroidal colobomas.

Our first approach, after determining that the retinal detachment was nonrhegmatogenous and that there was no demonstrable leak from the optic pit on fluorescein angiography, was to laser the peripapillary region and place the patient on strict bed rest. The subretinal fluid seemed to clear with reattachment of the retina and the development of a good chorioretinal adhesion in the peripapillary region. This appeared to work for a ten-month period. When the second retinal detachment occurred, it was much more extensive, consisting of a total bullous nonrhegmatogenous retinal detachment.

Preoperatively, the patient was retreated with laser photocoagulation in the peripapillary region through detached retina, thereby avoiding laser injury to the nerve fiber layer of retina. Then the subretinal fluid was drained to flatten the retina. A scleral buckle and an intravitreal air injection were given to further insure flattening of the retina and protect against a possible nonvisible peripheral retinal break in the coloboma area. The surgery appears to have worked with the retina still attached 18 months postoperatively. We think that in this case there may have been a communication over the optic pit region from the vitreous cavity to the subretinal space due to a dislocation of retinal tissue at the optic nerve head region (Fig. 2). The surgical treatment and laser photocoagulation approach was employed with this distinct possibility in mind. Unfortunately there is no way to clinically substantiate this possibility at this time.

In conclusion, patients with complete typical colobomas that have an associated optic pit may go on to develop retinal detachments that become complex management problems for the ophthalmic surgeon. Such cases may require a combination of argon laser photocoagulation treatment to the peripapillary region in conjunction with conventional scleral buckling surgical techniques to control the problem of recurrent retinal detachments in these patients.

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Student's Corner

Paul Celano, Editor

Prenatal Risk Assessment: An Evaluation of the Hobel Record in a Mount Sinai Clinic Population

STEPHEN WINTERS, B.A., STEVEN ITZKOWITZ, B.A., AND KENNETH JOHNSON, M.D.

Introduction

A poor neonatal outcome represents any medical or surgical condition present in the newborn that requires specialized care (for example, low Apgar score, prematurity, postmaturity, or too small or large for gestational age). Several methods have been devised to predict a poor neonatal outcome during the prenatal period (1–8). The methodology assigned arbitrary scores to selected prenatal factors that have been associated with poor neonatal outcome.

Among the various scoring systems, the one devised by Hobel et al, and subsequently modified by Hobel and Merkatz, seems to be the most comprehensive, specific, and objective(1). Risk factors which are assessed at the first prenatal visit, relate to the pregnant woman's past and current medical or obstetrical condition (hypertension, pulmonary disease, previous eclampsia, incompetent cervix). Developing problems are noted on subsequent prenatal visits. Two other subsets of the system relate to risk factors that occur during the intrapartum period and to the neonate. Risk factors were assigned values of one, five, or ten with a cumulative score of ten or more in either the prenatal or intrapartum period as a high-risk status. The value of a score of ten to discriminate between high and low risk was based on a study of the outcome of 715 pregnancies observed by Hobel during a 36-month period.

Nesbitt and Aubry developed a scoring system composed of eight major categories including maternal age, race, and parity, past obstetric and medical history, generative tract disorders, emotional and socioeconomic factors(2, 8). By assigning arbitrary risk values to items in the major categories, a Maternal Child Health Care Index score was generated for each patient by subtracting the total from a perfect score of 100. In a clinic population, 30% of pregnant women were scored as high-risk, while the corresponding value for private patients was 13%. Those scored as high-risk subsequently accounted for almost half of all poor neonatal outcomes and 60% of all maternal complications. The system devised by Nesbitt and Aubry did not include, in the assessment of risk, developing problems later in the prenatal period or in the intrapartum period.

Goodwin et al developed and evaluated another technique(3). The high-risk screening process of Goodwin consisted of three mean scores: 1) prenatal data including baseline facts and obstetric history, scored 0–3; 2) problems arising in the present pregnancy, scored 0–3; and 3) gestational age of the newborn, scored 0–4. When 936 pregnancies were evaluated by this system, those with higher scores accurately reflected those with greater potential risks. There was a highly significant correlation between abnormal 24-hour estriol values (a biochemical indicator of fetal growth) and the antepartum fetal risk scores in eighty-five cases. In addition, Yeh et al, using Goodwin's method, found a positive correlation between higher risk scores and lower Apgar scores, as well as greater arterial acidosis, of neonates born to 266 women(4). Although the Goodwin method could be used to estimate the potential of a pregnancy and the newborn to be at high-risk, it lacked an essential labor and delivery

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From the Department of Community Medicine, Mount Sinai School of Medicine of The City University of New York, New York, N. Y. 10029.

Requests for reprints should be sent to Kenneth Johnson, M.D., Department of Community Medicine, Mount Sinai School of Medicine, One Gustave Levy Place, New York, N.Y. 10029.

section and it evaluated the medical and past obstetric history less precisely than the Hobel system.

Coopland et al modelled a simple scoring system after Goodwin's technique and retrospectively studied 5,459 women admitted during labor at the University of Manitoba's teaching hospitals(5). A high risk score was found to correlate with an increasing percentage of poor neonatal outcomes. This method also lacked an intrapartum record and has been recommended for use on the first prenatal and thirty-sixth-gestational-week visits only.

Still another scoring system, developed by Effer in Canada, listed risk scores for one hundred fifty-five factors influencing pregnancy(6). At the onset of labor, a Prognostic Risk Score(PRS), based on the prenatal data, was coded for each patient. In his study, Effer found that increasing PRS scores correlated with abnormal one-minute Apgar scores. A standardized intrapartum data form was filled out, but there was no allowance for scoring of these data which might help predict poor neonatal outcome.

For the purposes of this study, the Hobel form was selected because it best approximated, in format and content, the clinical hospital record. The Hobel form allows for the precise recording of medical, obstetric, and surgical conditions during the past medical history, the course of the pregnancy and delivery, and the neonatal period. Further, as a problem-oriented medical record, it allows for facile identification of major medical problems.

Materials and Methods

The purpose of the study was to evaluate the usefulness of the Hobel risk assessment system in a predominantly Black-Hispanic group of clinic patients in New York City. Information was abstracted from completed clinical records for 64 pregnant women who delivered viable infants during the study period. Each patient was interviewed on the first postpartum day in reference to past medical/obstetric history, and events in the prenatal period corresponding to items on the Hobel form. Risk scores were totalled for the prenatal and intrapartum periods. Two nonEnglish speaking patients could not be interviewed because of the nonavailability of a translator, so comparison for the Item Analysis was made on only 62 patients.

In order to assess neonatal morbidity, any infant with one or more of the following criteria was defined as a poor neonatal outcome. These criteria were: 1) Apgar score of five or less at one minute or five minutes, 2) birth weight less than 2500 gm, 3) large for gestational age(Lubchenko/Dubowitz methods), 4) gestational age less than 37 weeks or 42 weeks or more, 5) developing medical problems in the neonatal period, and 6) Neonatal Intensive Care Unit(NICU) admission. Because infants that were admitted to the NICU represented the most serious cases of neonatal morbidity, these cases are described in the calculations as a subset of neonatal morbidity as well as in a separate category. During the study period one stillbirth occurred; this event was not included in the estimates of outcome since Hobel's methodology specifically excluded stillbirths.

Results

Comparison of items in clinical record and detected on interview

Patient interviews using the Hobel form detected prenatal information that was not recorded in the clinical records of 50 of the 62 individuals interviewed. Fourteen patients furnished information relating to historical items that were not recorded in their records and that would have placed them in a high-risk status at the time of the first prenatal visit. In order of frequency, the most common historical problems were a family history of diabetes and other illnesses, genitourinary infection prior to pregnancy, personal habits such as smoking, use of alcohol, and drug abuse, neonatal jaundice in a previous infant, and bleeding as a complication of a previous pregnancy. Unrecorded problems developing during the prenatal period were, in order of frequency, inappropriate maternal weight gain, genital-urinary conditions, psychosocial problems requiring social service, and bleeding after 20 weeks of pregnancy.

Distribution of risk scores

The distribution of the sum of risk scores for each of the 64 patients is shown in Figure 1. In this Black-Hispanic clinic population only three women were judged by Hobel's standard to be at low-risk (less than ten). The median score of the study group was 30.

Comparison of risk scores or clinical judgment to outcome

Table I demonstrates a positive relationship between prenatal risk scores and the relative frequency of NICU admissions and poor neonatal outcomes. There were no poor neonatal outcomes or NICU admissions for women

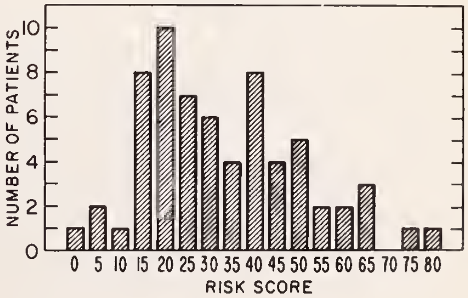

FIG. 1. Distribution of risk scores among the population studied.

TABLE I

Prenatal Estimates of Risk Related to Outcome

	Hobel Scores					High Risk (by clinical judgment)
	<10	≥10	≥25	≥40	≥55	
No. of patients (n=64)	3	61	42	26	9	13
No. of NICU admissions (n=18)	0	18(100%)	14(78%)	11(61%)	4(22%)	6(33%)
No. of poor neonatal outcomes (n=31)	0	31(100%)	23(74%)	16(52%)	7(23%)	6(19%)

scoring less than ten. Conversely, all of the NICU admissions and poor neonatal outcomes arose from women scoring ten or more. In fact, 61% of the NICU admissions and 52% of the poor neonatal outcomes came from women scoring 40 or more. These results contrast with the values obtained if only clinical judgment has been used to categorize patients as high-risk. The data show that only 13 women were considered high-risk and gave birth to only 33% of the NICU admissions and 19% of the poor neonatal outcomes. Thus, the majority of NICU admissions and poor neonatal outcomes arose from women considered to be at low-risk by clinical judgment.

As the risk cut-off score increased, the proportion of NICU admissions in the high-risk group also increased, with 30% (18/61) at a cut-off of ten, and 42% (11/26) at a cut-off of 40. The same trend applied to poor neonatal outcomes.

Sensitivity and specificity

Figure 2 demonstrates an expected inverse relationship between sensitivity and specificity as prenatal scores increase. In the study population the application of Hobel's criterion of ten or greater would have predicted all poor neonatal outcomes (sensitivity 100%) but at the expense of declaring all but three of the 64 patients at high-risk(specificity 9%). However, when a risk cut-off score of 40 was used, a sensitivity of 52% and specificity of 70% were obtained. These values most closely approximate those obtained from calculations on Hobel's original study(i.e., sensitivity 50%, specificity 69%).

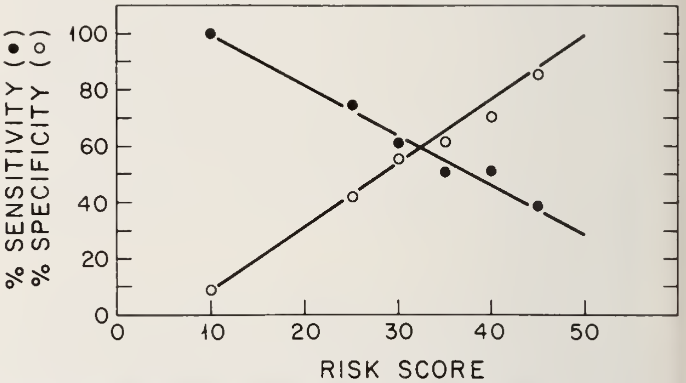

FIG. 2. Relationship between sensitivity and specificity as cut-off score increases.

Discussion

As indicated in the results, the Hobel problem-oriented record was able to gather more information than was present in the clinical records for 82% of the patients studied. For 27% of these patients, the additional information included historical factors that altered the risk categorization from low to high. Thus, the Hobel form appears to assure greater completeness of data collection compared to the relatively unstructured collection of data in the clinical record.

Even for the small population used in this study, the results suggested that higher risk scores may predict more poor neonatal outcomes. The present study is consistent with reports in the literature associating higher prenatal scores, by different techniques, with greater neonatal morbidity(1–6). The factors that we included in our poor neonatal outcome category were the same as those in other studies. Of the studies reported in the literature, only Coopland et al associated high risk scores with admission to the intensive care nursery(5). Using the Hobel scoring system, our findings indicated that there was a direct relationship between high-risk prenatal scores and subsequent NICU admission.

Although the Hobel method, used with a cut-off score of ten, detected all women giving birth to a poor neonatal outcome or NICU admission, it included many patients who gave rise to favorable outcomes. Applying Hobel's definition of risk as a score of ten or more, 95% of our population were considered at high-risk and accounted for 100% of the poor neonatal outcomes. The resulting high sensitivity of 100% and low specificity of 9% would have caused undue concern by placing too many women in the high-risk category and allocating unnecessary resources to them. To alleviate this concern, the efficiency of the technique could be increased by raising the risk cut-off. At a cut-off score of 40, 43% of the patients would be at high-risk and would give rise to 52% of all neonatal morbidity. The new sensitivity would fall to 52% but the specificity would increase markedly to 70%. The system would still be able to detect almost two-thirds of NICU admissions and over one-half of poor neonatal outcomes. If the cut-off of our study had been at 40, the sensitivity and specificity would have been almost identical to that Hobel obtained at a cut-off of ten. A possible explanation for this difference is that Hobel used a much larger population which may have differed considerably from the predominantly Black-Hispanic population used in our study.

In order for a woman to receive comprehensive care throughout her pregnancy, there must first be efficient screening to detect risk factors and then a formal protocol to manage any high-risk pregnancy. Several investigators have established protocols for the management of high-risk patients(6–12). High-risk obstetric and neonatal care should be managed by a special team consisting of internists, psychiatrists, obstetricians, and pediatricians, as well as ancillary personnel. Thus, while providing obvious advantages for the patient, there would be educational advantages for the medical staff and students. There would be the potential to make more frequent and better use of routine, as well as more specific, diagnostic tests.

The importance of trying to improve the outcome of pregnancy for all women in the U.S. has prompted the formation of a committee called the Committee on Perinatal Health (11). This committee, comprised of representatives from the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Medical Association, has developed a detailed schema for the establishment of regional perinatal health services throughout the U.S. The Hobel problem-oriented record could provide the necessary structure around which perinatal care could be organized. In terms of cost to the public, Merkatz and Johnson point out that a successful regionalization program using a precise scoring system could be expected to save money by decreasing the rate of NICU admissions and length of stay in such units(13).

From our study, it became clear that a cut-off score of 10 would result in a very high sensitivity but at the expense of a very low specificity. If a much larger clinic population could be followed from the first prenatal clinic visit through the neonatal period with this system, a thorough analysis of the most applicable factors could be made to determine which events are most predictive of neonatal outcome in the Mount Sinai clinic population, and an accurate division score between high and low risk could be determined.

Acknowledgements

We wish to thank Dr. Ed Speedling, Dr. Victor Knutzen, Dr. Thomas Kerenyi, the staff of the Departments of Obstetrics-Gynecology, Pediatrics, and Community Medicine, and Mrs. Ruth Katz and Mrs. Selena Viess for their assistance and cooperation.

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Submitted for publication January 1979.

ERRATUM

Several transcription errors appeared in our recent paper "Cancer in Universal and Left-Sided Ulcerative Colitis." (Vol. 46, Issue 1, pp. 25–32, 1979) Although these changes do not alter the sense of the paper, in the interest of accuracy we are submitting the corrected figures.

In Table II, the column headed "Expected cases" should read 0.0001, 0.0027, 0.0252, 0.0840, 0.4155, 0.8981, 2.7076, 4.13. The figures at the foot of the column headed Ratio Obs/Exp should read 6x.

In Table III, the column headed "Expected cases" should read 0.0001, 0.0019, 0.0171, 0.0505, 0.2221, 0.4635, 1.6231, 2.3783. The figure at the foot of column headed Ratio should read 9x.

In Table IV, the total for the column "Expected cases" should read 1.7550.

In the summary, paragraph two, line three should read "The O/E ratio among our UC patients was six with the ratio being nine in universal colitis and three in left sided colitis.

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Granulomatous Colitis*

RICHARD H. MARSHAK, M.D., ARTHUR E. LINDNER, M.D., and DANIEL MAKLANSKY, M.D.

In 1932 Crohn, Ginzburg, and Oppenheimer (1) first described the chronic granulomatous disease of the bowel that was termed regional enteritis. It was their belief that this was a disease of the terminal ileum, since such was the area of involvement in the 14 patients that made up their initial report. Only two years later, in 1934, Colp (2) reported the first case of granulomatous colitis in a patient who had involvement of both the cecum and the terminal ileum. Not much of the colon was involved, but the case was sufficient to demonstrate that the ileocecal valve is not a barrier to the development of disease in the colon. Subsequently, it has become apparent that Crohn's disease can involve any part of the digestive tract, from the mouth to the anus.

It was Morson and Lockhart-Mummery (3), of London's St. Marks Hospital, who in 1959 clearly defined the features of Crohn's disease of the colon and separated this entity from ulcerative colitis. The radiologic features of granulomatous colitis were later summarized by Marshak et al (4, 5).

The colon may become involved in the granulomatous process in several ways:

1. The colon alone may be the site of granulomatous disease.
2. Both the colon and the small bowel may be involved in granulomatous disease. In such patients the disease appears to begin at about the same time in the two areas, for both small bowel and colon are involved when the patient is first examined radiologically. It is uncommon to be able to document the spread of granulomatous disease from ileum to colon or colon to ileum in the absence of surgery.
3. The colon may become involved with granulomatous disease only after an ileocolic anastomosis has been performed for treatment of Crohn's disease of the small bowel (regional enteritis). The diseased segment of colon is almost always immediately adjacent to the anastomosis. The involved area may be small or extensive.
4. Finally, the colon may be involved directly by fistula formation from an adjacent loop of diseased small bowel. In our experience, such fistulas do not lead to granulomatous colitis. The inflammation does not usually spread, and the colonic lesion heals when the diseased small bowel has been removed and the fistula closed.

Clinical Features

Patients with granulomatous colitis, like those with ulcerative colitis, may have fever, abdominal cramps, diarrhea or constipation and, in children, growth retardation. Gross blood in the stools is unusual, however, and when it does occur it tends to be infrequent and not a prominent feature of the illness. Occult bleeding is often detected by examination of the stool with guaiac reagent and such blood loss contributes to the iron deficiency anemia that is frequently found. Perianal fistulas and inflammatory anal disease are common in granulomatous colitis and may appear before any of the other clinical features of the disease. Colonic involvement tends to be right-sided and segmental and the rectum is usually spared. Thus, a normal rectal mucosa on sigmoidoscopy in a patient with chronic inflammatory disease strongly suggests granulomatous disease. When the rectum is involved with Crohn's disease, distinction between ulcerative and granulomatous colitis may be difficult, but a sigmoidoscopic appearance of irregular and patchy inflammation points toward a diagnosis of Crohn's disease. Rectal biopsy may occasionally yield granulomas.

Fistulas, so characteristic a feature of regional enteritis, are also common in patients with granulomatous disease of the colon. They occur at some time during the course of the illness in about half the patients with Crohn's disease. Most of these fistulas are perianal in location. When internal fistulas are present, they usually arise from matted and adherent loops of diseased small bowel and may extend into the colon. Fistulas originating in the colon are less common.

Extraintestinal manifestations, such as uveitis, arthritis, erythema nodosum and pyoderma gangrenosum, occur in granulomatous colitis just as in ulcerative colitis. But in contrast to the well-known malignant potential of ulcerative colitis, carcinoma of the colon is not common in association with granulomatous colitis (6). This may reflect in part the influence of early surgical resection in the management of Crohn's disease. In this regard, there have been a number of reports of carcinoma of the small bowel occurring in patients with longstanding, chronic regional enteritis or with bypassed intestinal loops (7).

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* From the forthcoming text, Radiology of the Colon, to be published by W. B. Saunders Co.

From the Departments of Radiology and Medicine, Mount Sinai School of Medicine of The City University of New York, N.Y.

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In further contrast to ulcerative colitis, free perforation of the large bowel and toxic dilatation are less frequent (8). The pathology of Crohn's disease, with thickening of the bowel wall by edema and fibrosis, would seem to militate against these acute complications.

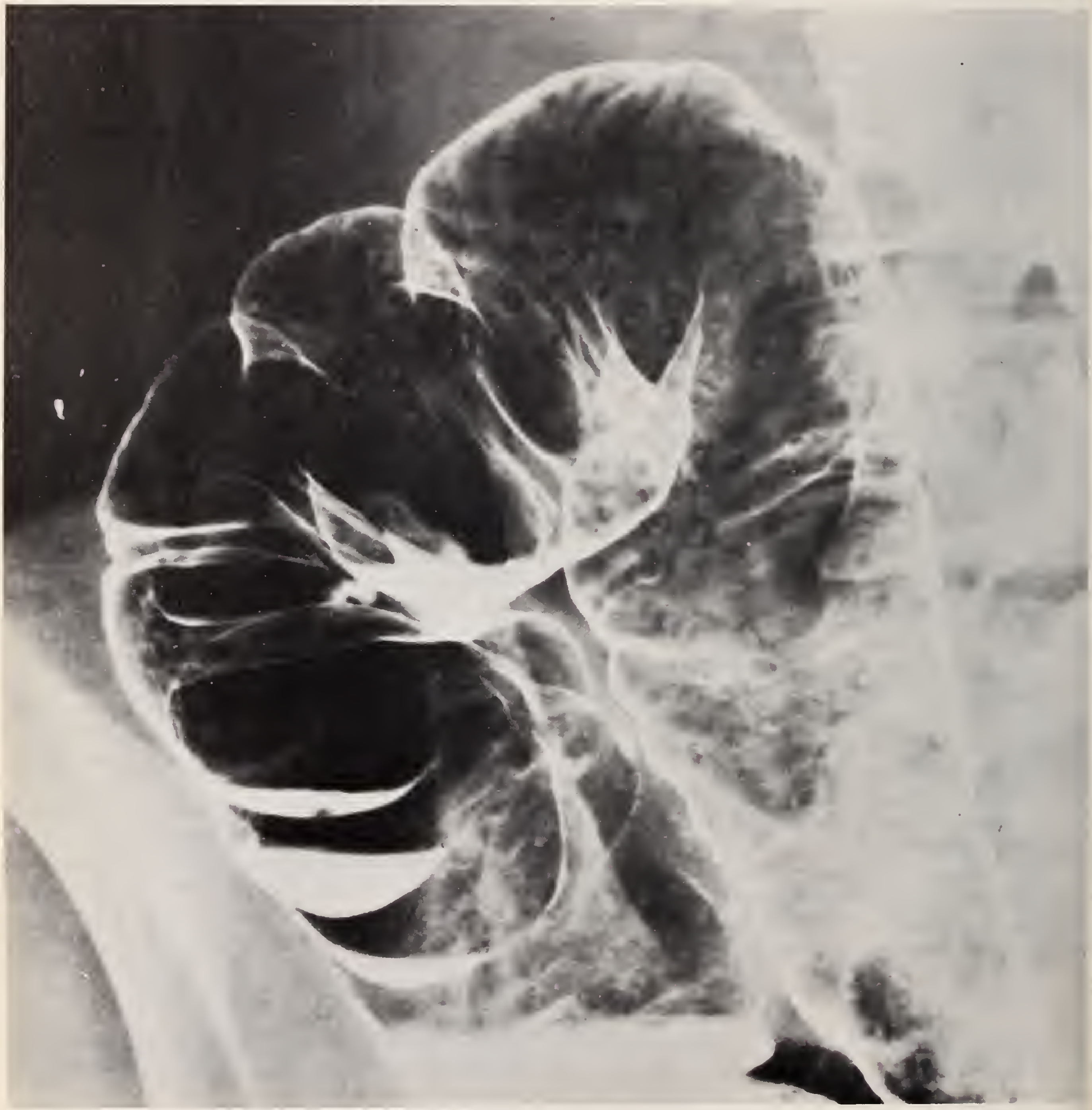


FIG. 1. Granulomatous colitis. Apthoid ulcers in the hepatic flexure are demonstrated on air contrast studies. The ulcers appear as tiny radiopaque densities surrounded by radiolucent halos. (Courtesy Dr. I. Laufer.)

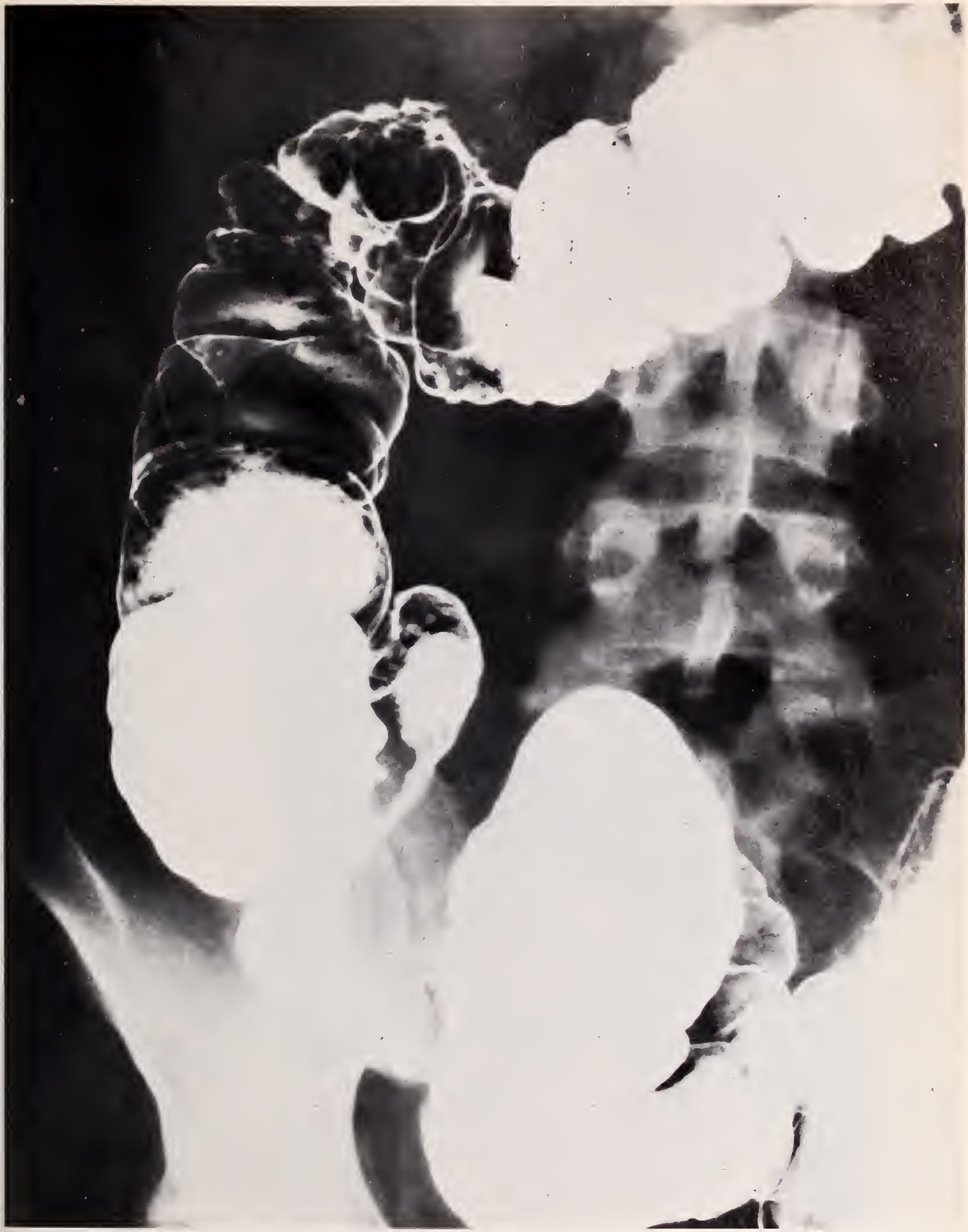


FIG. 2. Granulomatous colitis. Apthoid ulcers in the ascending colon and punched out ulcers in the hepatic flexure. The terminal ileum is also involved. (Courtesy Dr. I. Laufer.)

Pathology

The pathology of granulomatous colitis is that of Crohn's disease elsewhere in the gastrointestinal tract. There is a chronic inflammation extending through the entire wall, involving especially the submucosa. The bowel wall is thick and rigid, with narrowing of the lumen that may lead to stricture formation. Ulcers are deep and tend to appear as long linear ulcerations intersecting with deep transverse fissures. The intervening mucosa is swollen and the luminal surface has a coarsely nodular appearance that has been likened to a cobblestone road. Involvement of the bowel wall may be asymmetrical rather than circumferential. Segments of involved gut are adherent to each other or to loops of normal bowel and colon may be included in the inflammatory mass. Fistulas between segments of bowel or to other viscera are often seen and intraabdominal abscesses may be present. When the ileum as well as the colon are involved in this inflammatory process, the condition is called granulomatous ileocolitis.

In the opinion of some pathologists, the earliest lesions are small white-based ulcerations that have been termed "apthoid ulcers." These ulcers, that may be overlooked if the mucosa is not carefully examined, have been noted near the edges of a resection and may be the initial stage of recurrence of disease. Experience suggests that these early lesions may take years to progress to a state of sufficient structural damage to give rise to detectable clinical or radiologic signs. Therefore, these apthoid ulcers do not require extension of surgery beyond the major lesion. They begin as a central micro-abscess that develops within aggregates of lymphoid tissue at the lower levels of the mucosa. Apthoid ulcers are probably the forerunners of the punched-out ulcerations and the longitudinal ulcers and transverse fissures that characterize the late stages of Crohn's disease.

Histologic examination in established disease shows a chronic inflammatory reaction most prominent in the submucosa but extending through the bowel wall, with edema and fibrosis. The ulcerations are deep and may extend through the serosa as small sealed-off perforations to which adjacent viscera may adhere. The characteristic histological feature is the presence of noncaseating granulomas with Langhans' giant cells and epithelioid cells. Especially when ulceration is severe or when the patient

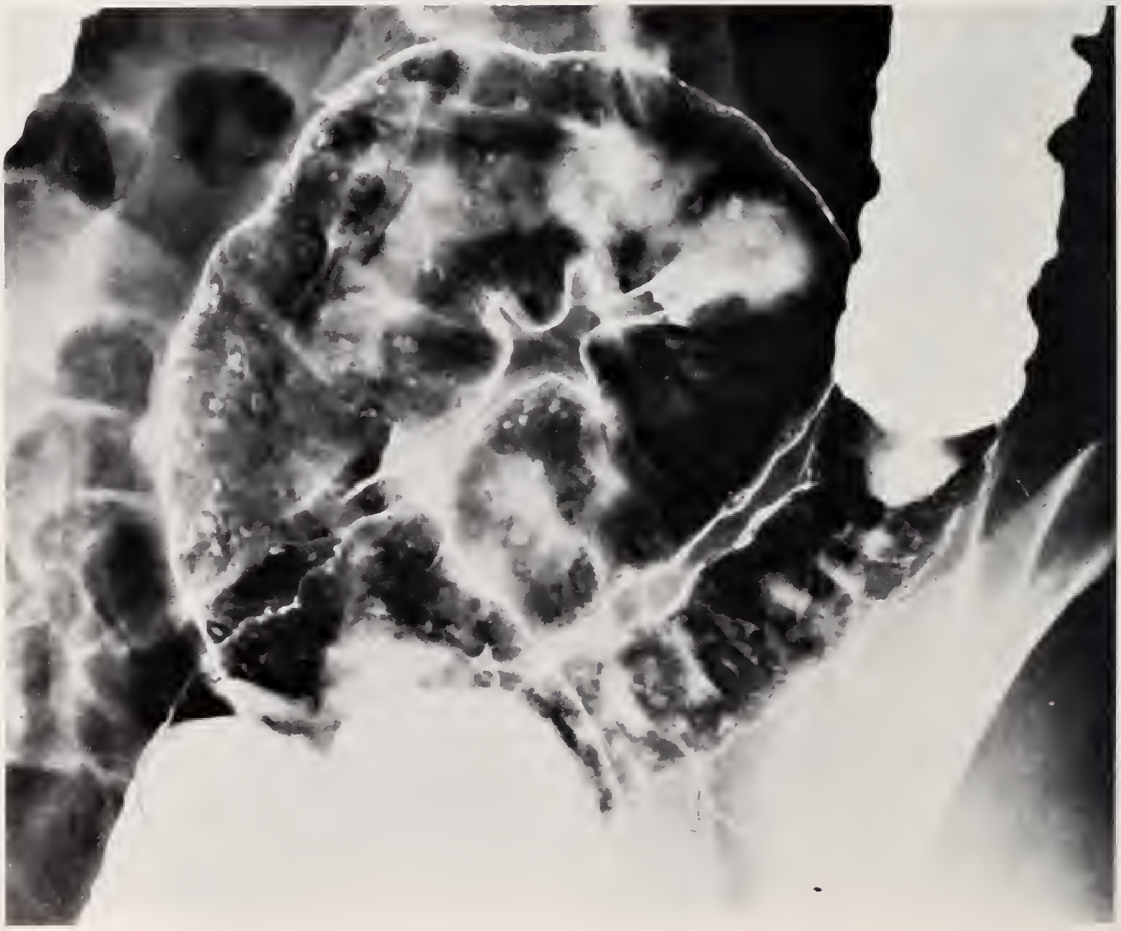


FIG. 3. Apthoid ulcers in the sigmoid. (Courtesy Dr. C. Bartram.)

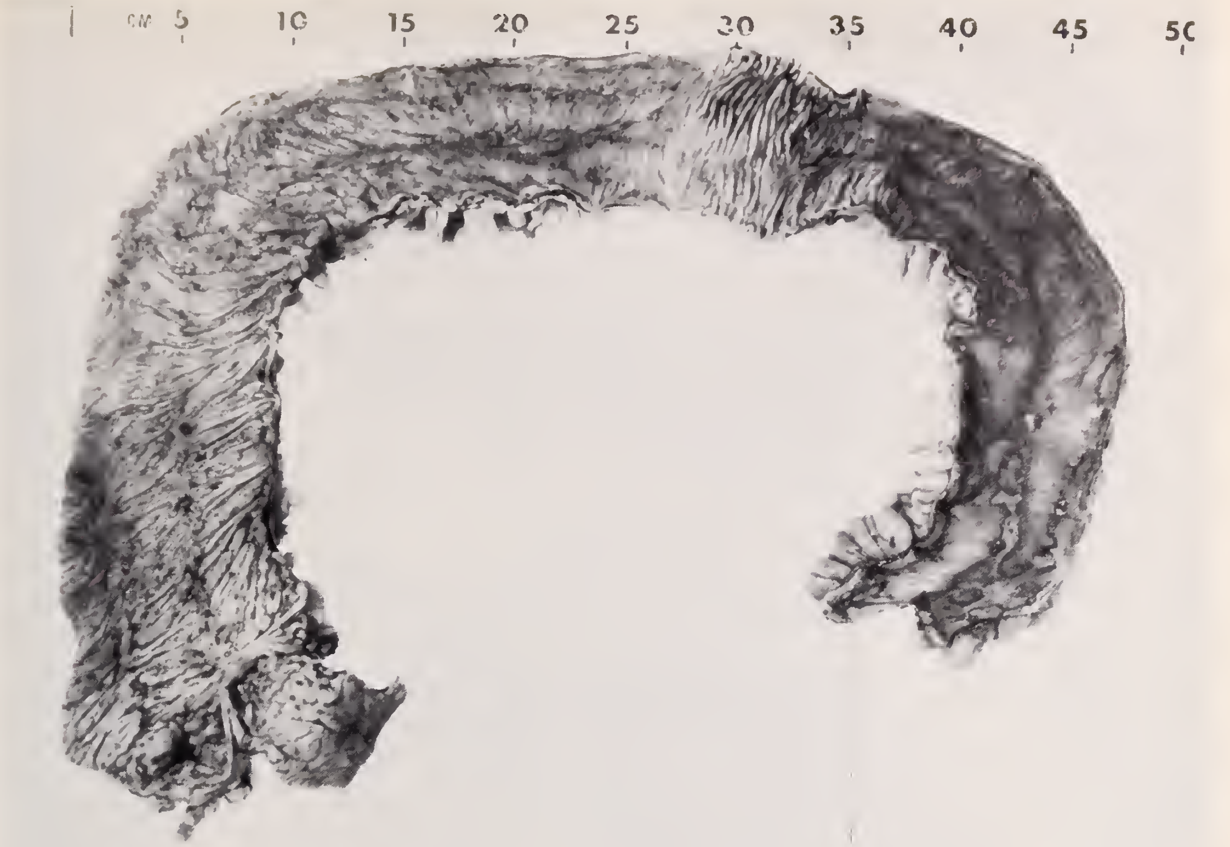


FIG. 4. Granulomatous colitis. Specimen showing apthoid ulcers, punched out ulcers, skip lesions, longitudinal and transverse ulcerations, and early cobblestoning. (Courtesy Dr. B. Morson.)

has been treated with corticosteroids, granulomas may be scant or even absent. Most pathologists agree that a diagnosis of Crohn's disease is warranted if the other typical pathologic features are present. Regional lymph nodes may be enlarged and on section show the presence of granulomas.

Medical and Surgical Treatment

The goal of medical treatment in granulomatous colitis and ileocolitis is to induce full clinical remission. Unfortunately, sustained remissions are uncommon in granulomatous disease, and often the physician finds that his task is to make the patient as comfortable as possible, functioning in daily life despite the activity of a chronic illness.

The medical treatment of granulomatous colitis does not differ from that of ulcerative colitis in any important respect. Supportive treatment that is appropriate for all patients includes: dietary manipulation to avoid foods to which the patient in his own experience is intolerant, adequate rest, sedation as needed, antidiarrheal agents such as the opiates, correction of anemia, which usually can be accomplished with iron, and—perhaps as important as any of these—supportive psychotherapy by the internist or gastroenterologist.

Sulfasalazine (Azulfidine) is sometimes employed as an antiinflammatory agent in Crohn's disease just as in ulcerative colitis but in general the drug does not seem as effective as in the latter disease. Studies are now underway to evaluate in a controlled fashion the effectiveness of Azathioprine (Imuran), a drug that has both immunsuppressive and antiinflammatory properties. In patients with extensive small bowel involvement or debilitating fistulas, hyperalimentation may provide temporary relief of symptoms and an opportunity for effective use of other drugs and therapies (9).

The adrenocortical steroids are useful in the management of symptoms although there is no evidence that steroids alter the natural history of the disease. Many experienced physicians withhold steroids as long as possible in the course of the illness and rely upon combinations of supportive measures. Steroids are employed when the clinical condition is deteriorating or when symptoms persist for prolonged periods. In considering the type of steroid therapy to be employed, both the

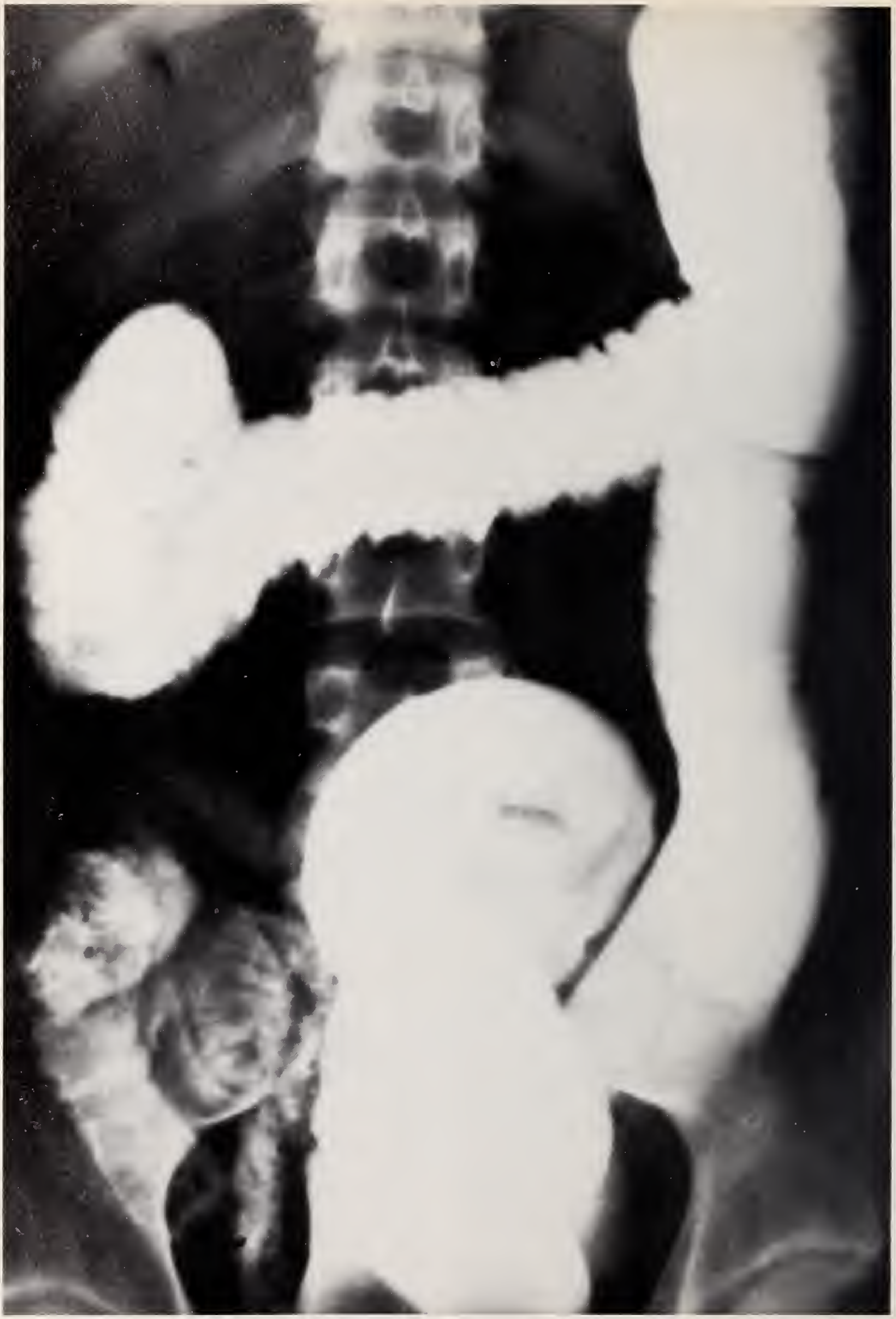


FIG. 5. There are numerous small irregular nodular defects along the contour of the transverse colon associated with minimal rigidity. Th cecum and ascending colon are spastic and irritable.

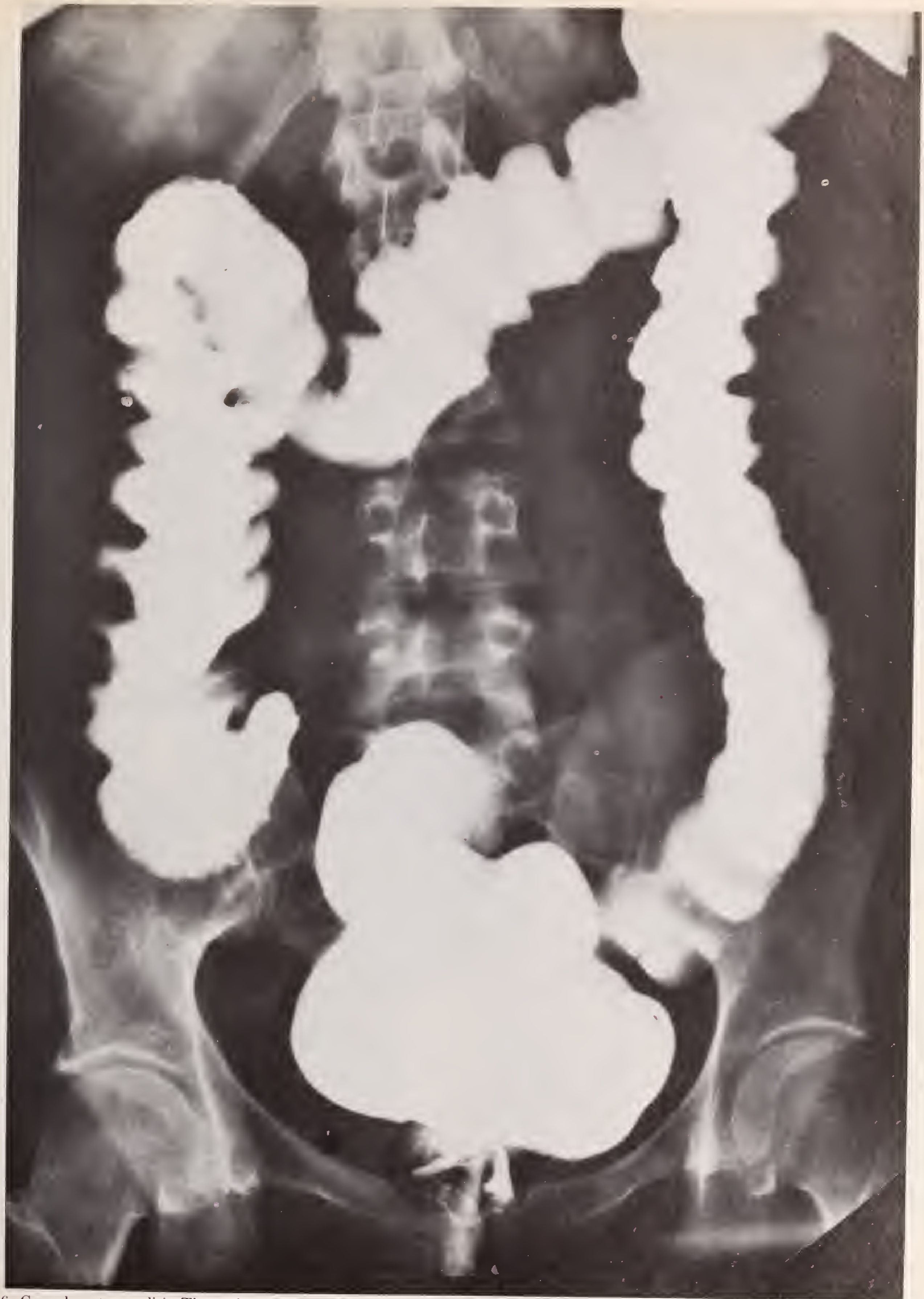


FIG. 6. Granulomatous colitis. The entire colon except the rectum is involved with numerous small nodular defects associated with tiny ulcers. The haustral markings are thickened. The colon is moderately spatic and irritable.

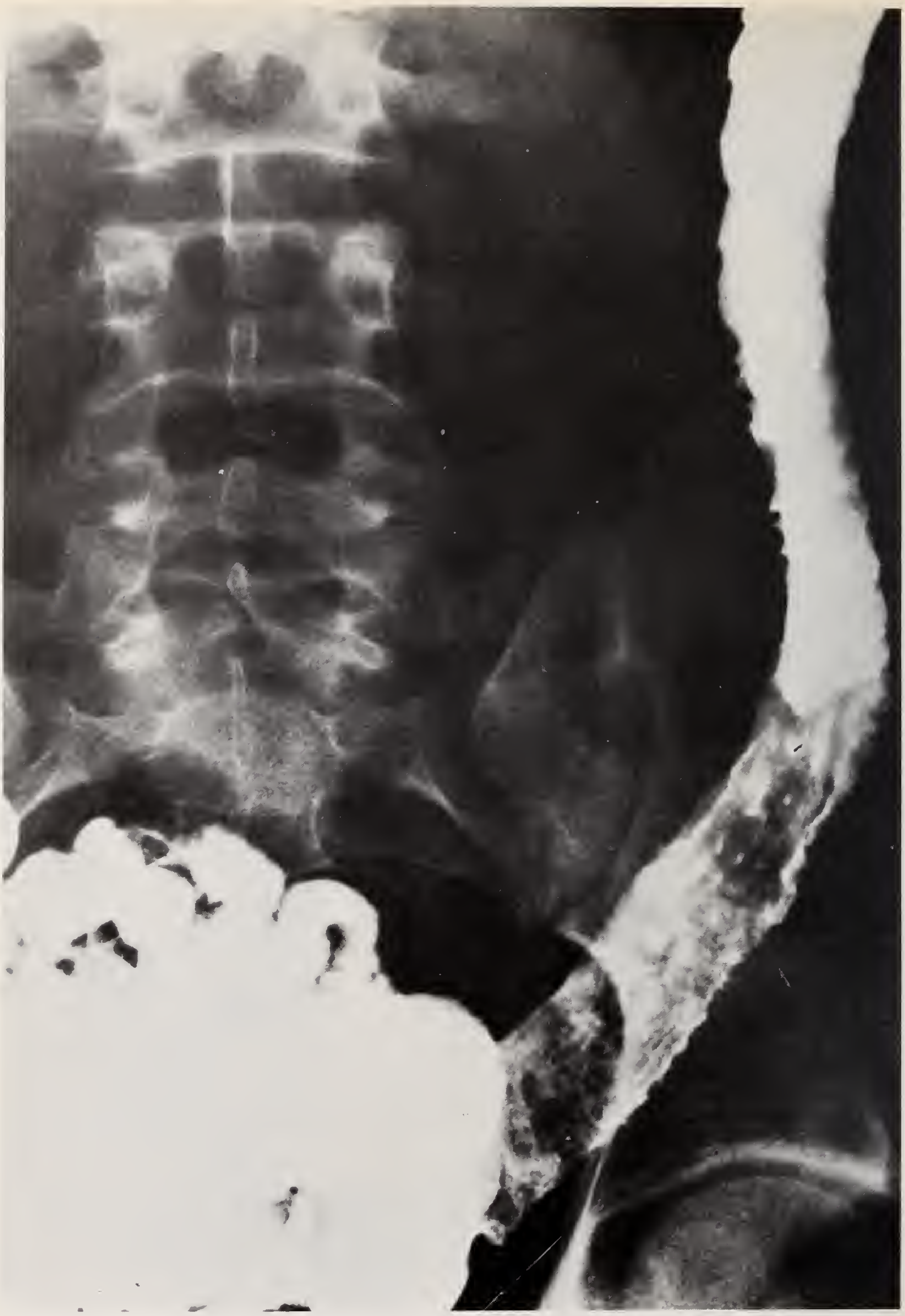


FIG. 7. Granulomatous colitis. There are numerous small ulcerations within the lumen and along the contours of the bowel in the region of th distal descending colon. There is slight narrowing and rigidity.

severity and the location of the disease should be taken into account. When the illness is of moderate degree, prednisone or related oral drugs are administered. When the patient is severely ill, intravenous ACTH may be the treatment of choice, just as in severe ulcerative colitis. If the rectum is involved, rectal instillation of steroids, either alone or in conjunction with oral steroids, may be of benefit.

Surgery is indicated for treatment of the complications of granulomatous colitis. The indications include obstruction, fistulas which are symptomatic or causing debility, abdominal masses and abscesses unresponsive to medical management, and the very rare complications of perforation or massive hemorrhage. Usually obstruction and infection with abscess formation are the complications that require surgical intervention. "Intractability" to a medical program, without development of complications, is a difficult surgical indication to define, but it is a real one. It embraces patients who, despite good medical management, simply do not do well. They have progressive disability with diarrhea, abdominal pain, fever or chronic illness. In this group one must consider treating the disease surgically.

The considerations of surgery in granulomatous disease are complicated by the threat of recurrence of inflammatory disease in the months or years postoperatively, for the contemplated surgery may not be curative. It is an interesting but unexplained observation that recurrences appear to be less common when only the colon is diseased. In ileocolitis, however, with disease in both small bowel and colon, development of granulomatous disease in what appeared to be normal small bowel or colon often occurs following resection of the involved gut. As a general rule in the management of granulomatous disease, many gastroenterologists believe that surgery should be deferred in favor of medical treatment as long as possible. Nevertheless, surgery is ultimately required, or deemed desirable, in most patients during the course of their disease. Recurrent disease is managed on the same principles as the original inflammatory process, with medical treatment employed as long as possible and reresection reserved for complications.

When surgical intervention is required, the choice of procedure is influenced by the location of the disease. Since the rectum is often spared, subtotal colectomy with ileoproctostomy may prove feasible. When all or most of the colon is involved, or when anal disease is severe, ileostomy and total colectomy is required. Patients with ileocolitis are highly susceptible to recurrent disease and long segments of small bowel and colon are often involved. Such patients are usually best managed supportively on medical programs. When surgical intervention is required, the minimum possible resection is recommended.

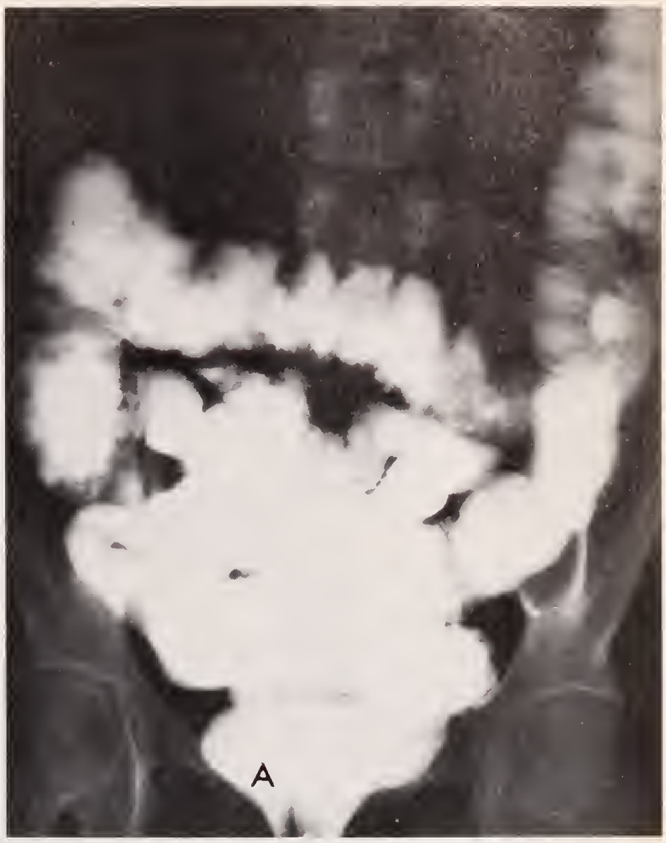


FIG. 8a. Granulomatous colitis. There is involvement of the colon from the cecum to the splenic flexure characterized by irregularity of the contours with multiple small nodular defects. The findings are most marked in the distal transverse colon where there is rigidity and lack of distensibility.

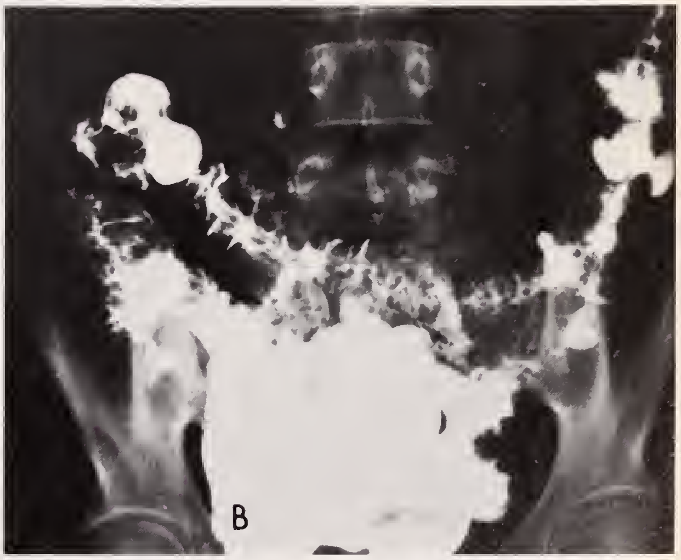


FIG. 8b. Evacuation film of 8a. The mucosal pattern has an irregular nodular appearance. Small skip lesions indicated by pseudodiverticula are identified. Involvement of the left side of the colon not appreciated on Fig. 8a is well demonstrated on this film, again showing the value of an evacuation film in granulomatous colitis.

Technique of Barium Enema Examination

Our technique is similar for the various types of inflammatory bowel disease. Because diarrhea is usually moderately severe, we prefer to avoid laxatives. Many patients use antidiarrheal agents and at times constipation may occur, accompanied by large numbers of fecoliths. In such individuals, gentle cleansing with laxatives becomes necessary. In the typical patient, however, with multiple bowel movements during the day, we suggest the following: a liquid diet for two days, followed by tap water enemas until the returns are clear. Many patients have difficulty in retaining barium and administration of glucagon is helpful for muscle relaxation just prior to the examination. In fulminant or very active disease barium enema examination should be deferred until symptoms have subsided.

There has been some discussion in the literature concerning the technical method that best demonstrates the roentgen findings in inflammatory bowel disease. There are two basic methods for performing barium enema examinations. First is the conventional, filled colon examination with barium sulfate mixtures utilizing high KV and multiple compression spot films. It is important that the barium-water mixture not be too dilute and that it contain a good suspending agent. Good evacuation films are regularly obtained.

The second method is a double contrast technique (10) using high density barium to coat the bowel, with the immediate injection of air, resulting in high quality air contrast films. Multiple projections are employed, including upright and lateral decubitus studies.

Both of these methods are excellent. The double contrast method is superior for the detection of tiny or apthoid ulcers but a good evacuation film cannot be obtained. All the other roentgen alterations can be well identified with either method.

Our current procedure in inflammatory bowel disease is as follows. The initial examination is the conventional filled colon technique as outlined above. This method demonstrates such functional abnormalities as spasm, irritability, increased secretions and areas of minimal rigidity. If the initial examination is normal but the patient's history is suggestive of inflammatory bowel disease, the patient returns the next day for the high density barium double contrast study to search for tiny ulcers. With this dual technique the roentgen diagnosis of inflammatory bowel disease is highly accurate.

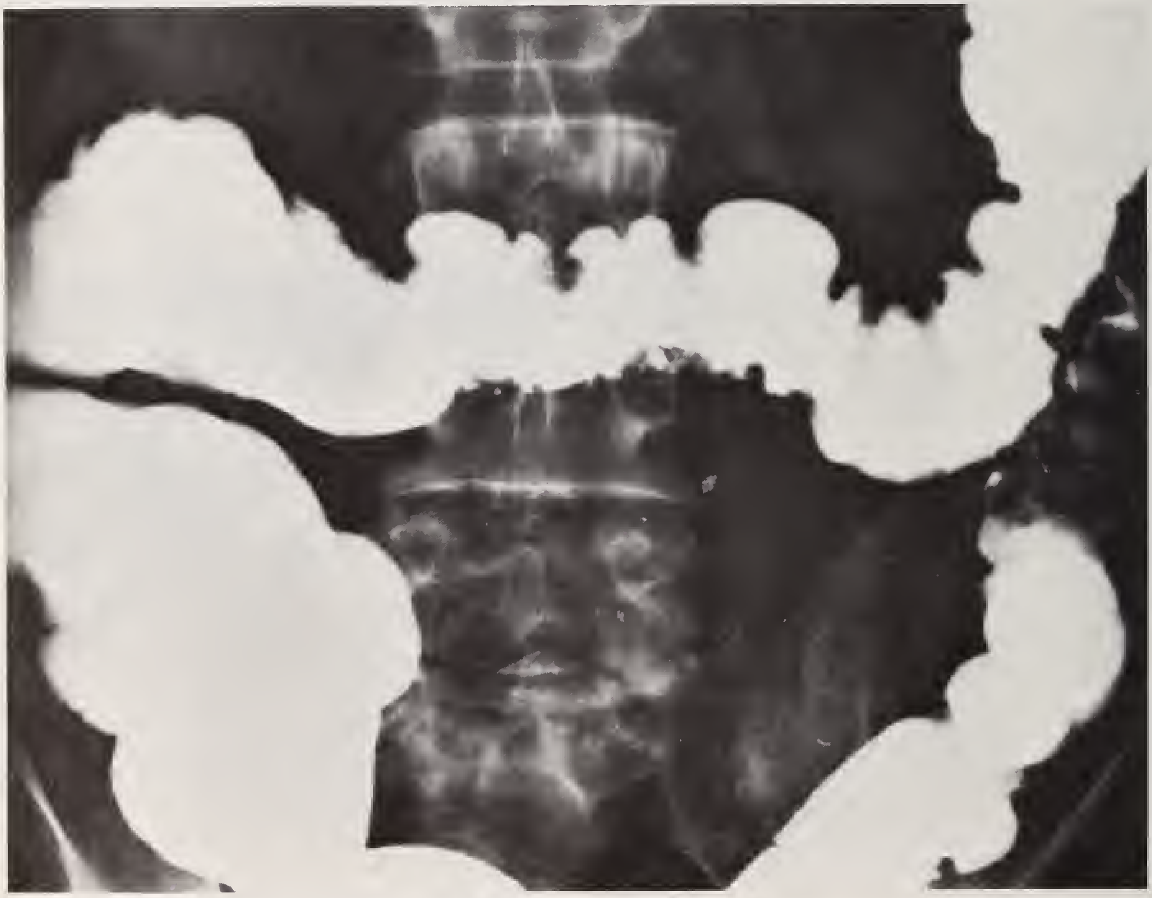


FIG. 9. Granulomatous colitis. There are multiple punched out ulcers seen along the inferior aspect of the transverse colon associated with pseudodiverticula, narrowing, rigidity and thickening of the haustra.

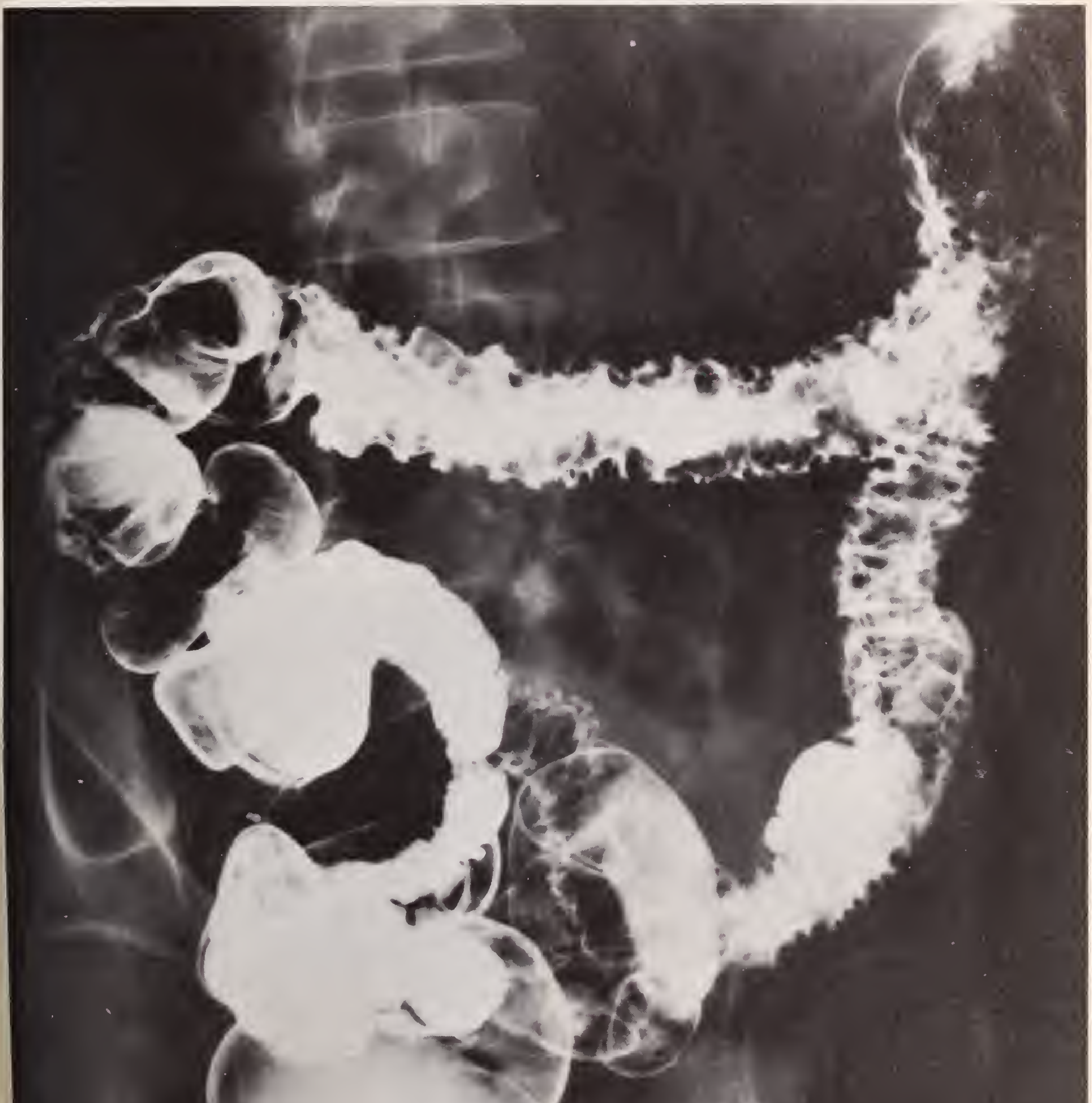


Fig. 10. Grannulomatous colitis. Multiple ulcerations are associated with a moderate degree of narrowing and rigidity. The terminal ileum and tum are normal.

Roentgen Features

One of the striking radiologic features of granulomatous colitis is the frequency of concomitant and similar disease in the small bowel. Indeed, 85% of the patients we have studied with granulomatous disease involving the colon have disease of both ileum and colon. In 15% the disease is confined to the large bowel. The most frequent distribution we have seen in granulomatous colitis is involvement of the terminal ileum and the colon to the splenic flexure or the sigmoid with sparing of the rectum. Universal involvement of the colon including the rectum is noted in 10%–15% of patients.

The radiologic features characteristic of granulomatous colitis are those that have been recognized in the small bowel in patients with regional enteritis. These findings include tiny ulcers (apthae), punched-out ulcers, small nodular defects, skip lesions, contour defects, longitudinal ulcers, transverse fissures, deep and ragged ulcers (abscesses), eccentric involvement, pseudodiverticula, narrowing and stricture formation, pseudopolypoid changes with a coarse and cobblestone-like mucosal pattern, sinus tracts and fistulas.

The earliest roentgen findings in granulomatous colitis are tiny ulcerations (Figs. 1–4) (11–13). Apthoid ulcers are best demonstrated with air contrast studies utilizing high density barium and glucagon where they appear as a small central barium density surrounded by a radiolucent halo. On the single contrast study these ulcerations appear as tiny specks within the lumen, tiny spicules projecting from the contours of the bowel, or tiny ulcers within irregular nodules (Figs. 5–7). The nodules are secondary to lymphoid hyperplasia and obstructive lymphedema.

Other early roentgen alterations include thickening of the haustral septae, slight rigidity, and increased secretions. These alterations may be diffuse, confined to a short segment, or seen in the form of multiple lesions with normal intervening bowel (skip lesions).

The mucosal pattern after evacuation is helpful in demonstrating thickening or nodularity of the mucosa. It should be noted that postevacuation films cannot be obtained after air contrast studies (Figs. 8a,b). Also of value is a film to follow the barium through the colon as part of the small bowel examination. This film may detect early changes not recognized in the filled colon or on air contrast studies.

On occasion, ulcerations are suggested by straightening or rigidity of a segment of bowel associated with pseudodiverticula on the opposite wall (Fig. 8b). Pseudodiverticula are created by involvement of one wall of a segment of bowel but not the opposite wall. Ulceration produces spasm and contractions but the opposite, uninvolved wall becomes folded creating the appearance of diverticula (eccentric skip lesions).

The tiny ulcers (apthae) grow larger and become irregular punched-out ulcers (Figs. 9, 10b) that combine t produce longitudinal and transverse fissures. The inflamed mucosa between the longitudinal and transvers fissures produce a cobblestone pattern (Figs. 11a,b). Cobblestoning does not always indicate ulcerations and ma also represent barium caught between edematous mucosal folds, compartmentalized by underlying fibrosis.

Deep collar button ulcers are seen as often in granulomatous as in ulcerative colitis (Fig. 12). They may als be found in ischemia of the colon and in amebiasis. Ulcer may penetrate beyond the contour of the bowel an appear in profile as numerous long spicules perpendicula to the long axis of the bowel. Localized abscesses ma occur producing rounded sac-like structures simulatin diverticula. When the fissures penetrate into adjacen loops, a fistula is formed (Figs. 13a,b,c,d,e). In the late stages of the disease, the entire mucosa may be slough because of diffuse ulcerations. In those cases in whic the bowel is diffusely and symmetrically involved an there are no typical features of granulomatous disease differentiation from ulcerative colitis may be impossibl especially in the absence of characteristic features in th small intestine (Fig. 14). Another diagnostic proble

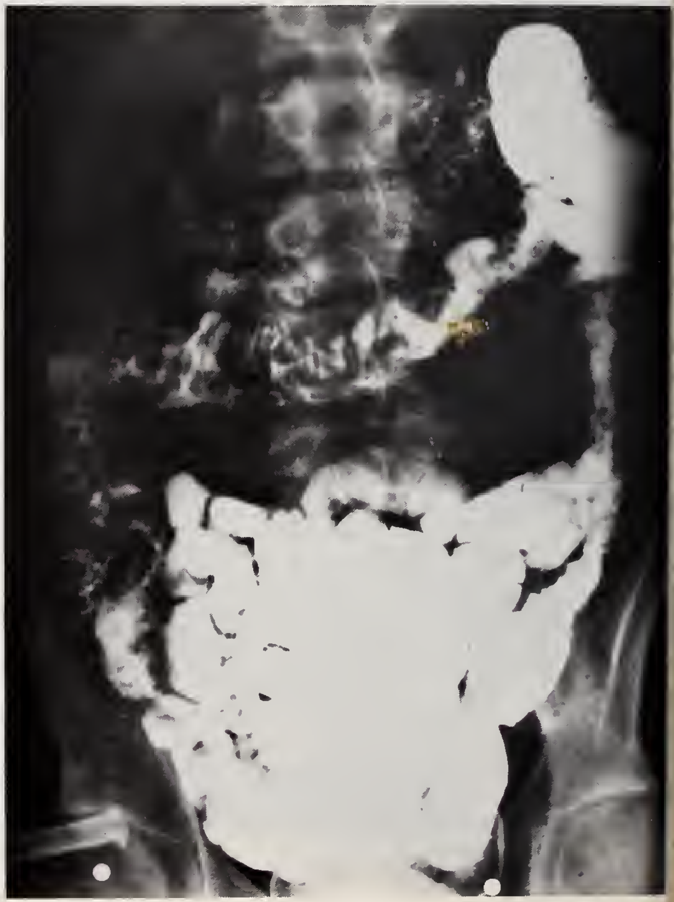


FIG. 11a. Granulomatous ileocolitis. There is cobblestoning pr duced by longitudinal and transverse ulcerations with narrowing an rigidity of the colon. The findings in the colon and ileum are identic

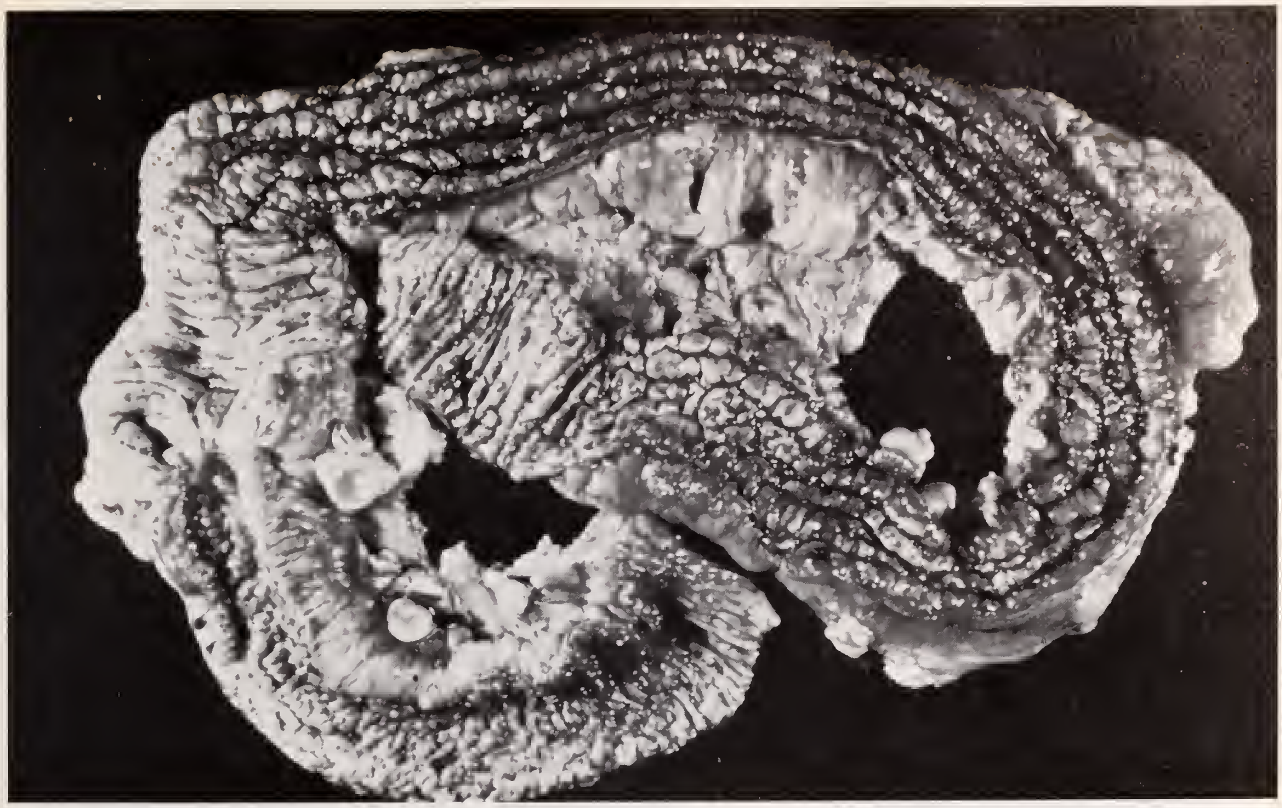


FIG. 11b. Specimen of Fig. 11a. Granulomatous ileocolitis. The longitudinal and transverse ulcerations in the distal ileum and colon formed a cobblestoned mucosa. Note also the enlarged mesenteric lymph nodes.

arises when only the rectum and sigmoid or left colon are involved in granulomatous disease. These cases can be distinguished from ulcerative colitis only if characteristic radiologic features of granulomatous disease are present within the area of involvement (Fig. 15).

In some patients, large irregular nodular contour defects with hazy margins are seen (Fig. 16). These lesions primarily reflect mucosal and submucosal edema associated with ulcerations. Large inflammatory polyps may also be identified. When multiple, these may simulate a neoplasm or cause obstruction (Figs. 17a,b,c) (14). At all stages of the disease, skip lesions may be identified. Thickening of the bowel produces irregular stenotic segments and strictures (Fig. 18). Rarely is granulomatous colitis seen as a single stricture of the colon. When this stricture is eccentric and associated with suggestions of overhanging edges, differentiation from carcinoma may be impossible. In most cases, however, there is further evidence of involvement of the bowel in the form of skip lesions, strictures, or other identifying features of granulomatous disease.

Granulomatous Ileocolitis

The radiologic features of granulomatous ileocolitis are those of granulomatous colitis in the colon and of regional enteritis in the small bowel (Figs. 6, 11a, 19). The characteristic findings of regional enteritis are not affected by the presence of concomitant inflammatory disease in the colon. In most cases, the inflammatory process in the small bowel is confined to the terminal ileum, but at times long segments of small bowel are involved.

Granulomatous ilecolitis must be distinguished from backwash ileitis associated with ulcerative colitis. In backwash ileitis, narrowing of the intestinal lumen is usually minimal and the length of ileum involved is small. Sinus tracts, skip areas, and fistulas are not seen; and the mucosa is only slightly altered, with minimal thickening of the folds. In a rare case, differentiation is impossible. In patients with ileocolitis, the involvement of the colon is usually in continuity with the disease of the ileum.

Carcinoma of the Colon in Crohn's Disease of the Colon

Although ulcerative colitis must be considered a premalignant lesion because there is a clear tendency for carcinoma to develop in the bowel involved with that disease, it is less common for colonic carcinoma to arise in patients with granulomatous colitis. Several cases, however, have been reported (6).

Reports of carcinoma of the small bowel in association

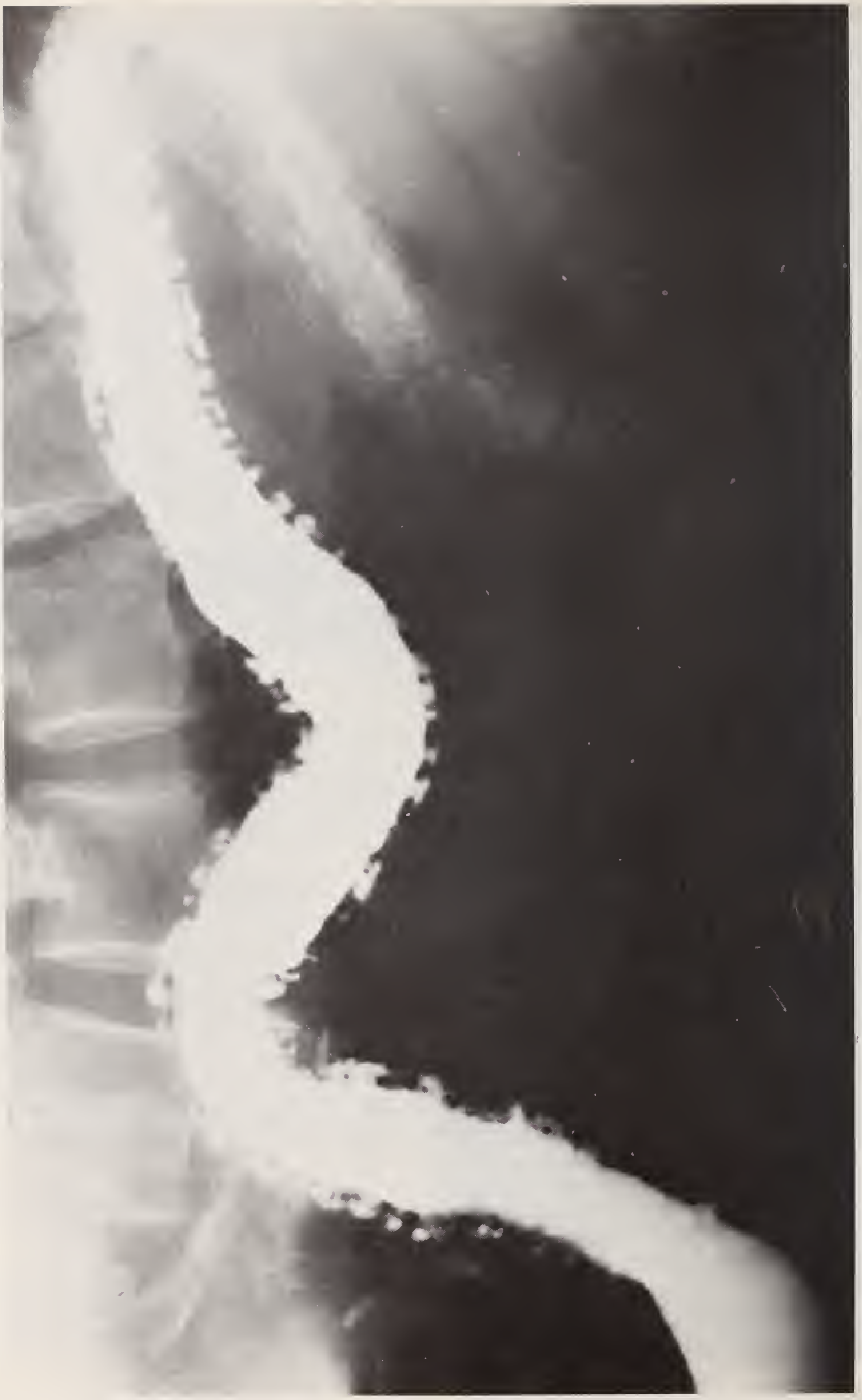


FIG. 12. Granulomatous colitis. Collar-button ulcers are identified projecting from the anterior and posterior wall of the descending colon sigmoid.

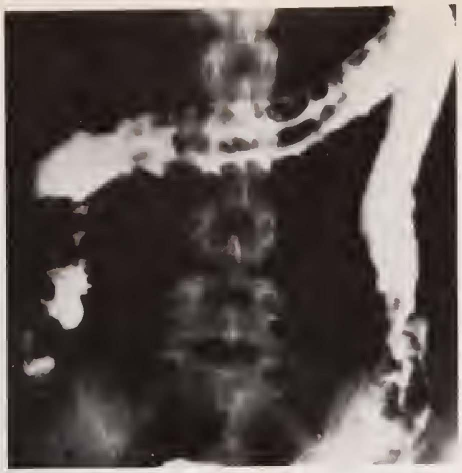


FIG. 13a. Granulomatous colitis. There are longitudinal ulcerations and transverse ulcerations in the transverse colon.

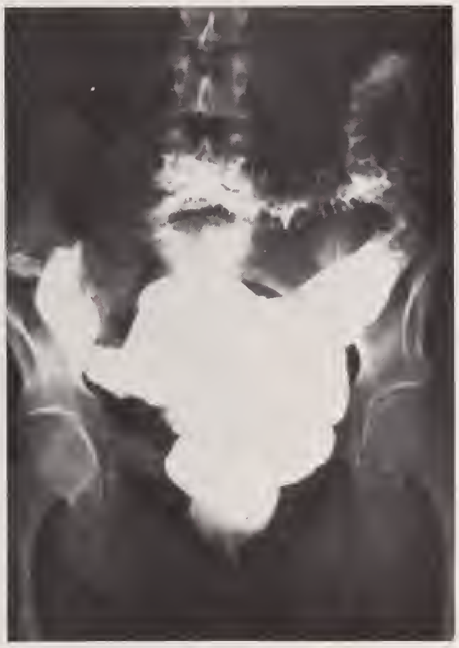


FIG. 13b. Same patient as Fig. 13a. A film taken six months after that shown in Fig. 13a reveals extensive ulceration of the colon from the cecum to the middescending colon. In the transverse colon there are marked transverse ulcerations. The terminal ileum is also involved. The rectum, sigmoid and lower descending colon are normal.

with regional enteritis are well known (7). In these cases, the carcinoma in the small bowel has usually developed either in areas of longstanding disease with stricture formation or in a bypassed segment. Enough cases have now been reported to suggest that the incidence of carcinoma of the small bowel is greater in patients with regional enteritis than in the normal population. The fewer instances of carcinoma reported in Crohn's colitis may reflect earlier surgery in colonic disease.

In the few cases that have been described, the carcinoma of the colon presented typical malignant features but was difficult to isolate from adjoining severe inflammatory disease. In most patients the diagnosis of carcinoma has been established only at laparotomy or autopsy.

Toxic Dilatation of the Colon in Crohn's Disease of the Colon

The colon involved with granulomatous colitis would appear to be an unlikely candidate for development of severe dilatation and threatened perforation because the

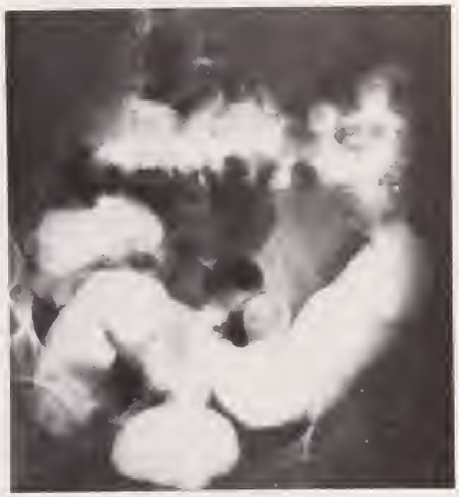


FIG. 13c. Same patient as Figs. 12a and b. Numerous sac-like ulcerations simulating diverticula extend from the contour of the transverse colon.

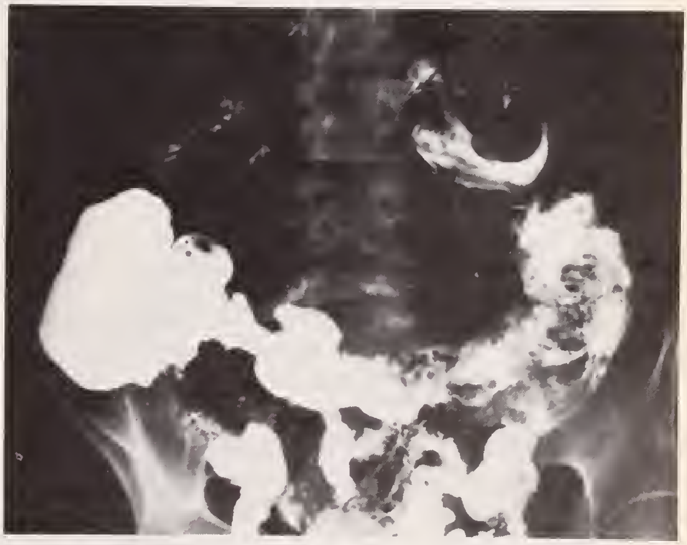


FIG. 13d. Same case as 13a two years after the original study. There is more extensive involvement of the colon with a fistulous communication between the splenic flexure and the stomach. The distal transverse colon is ulcerated with gross irregularity of the contours.

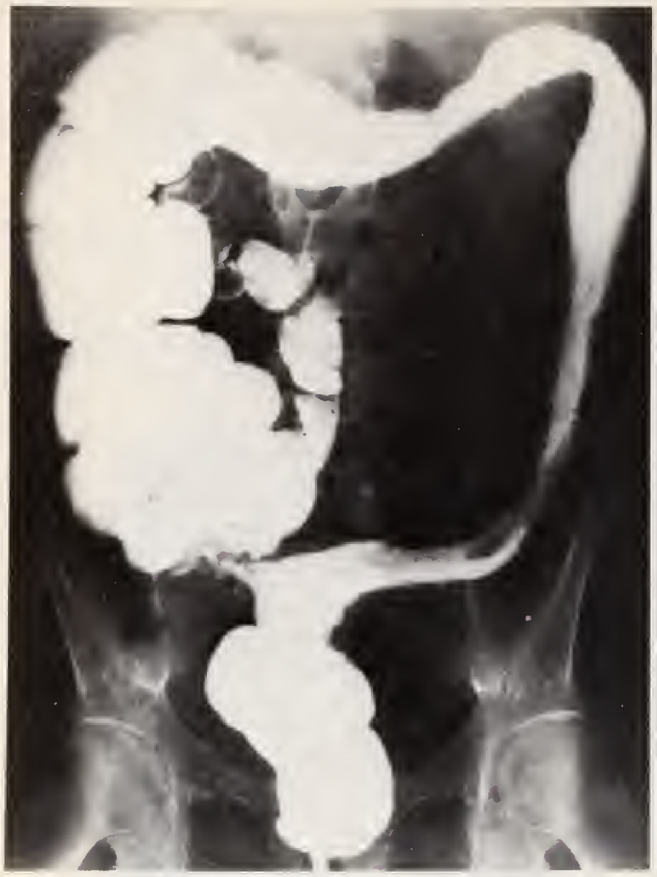


FIG. 13e. Granulomatous colitis. There is a fistulous communication between the distal ileum, cecum and sigmoid.

chronic inflammation is transmural and tends to thicken the wall. However, in more active and early forms of the disease, before fibrosis has become a conspicuous feature, moderate degrees of dilatation have been observed (8). These cases are frequently associated with deep abscesses and sinus tracts and the findings have usually been confined to the transverse colon. The markedly distended colon observed in toxic dilatation of ulcerative colitis has not been seen in our patients.

Recurrences and Linear Extension of Disease

Granulomatous disease may cause progressively more severe inflammatory changes within its area of involvement. Minimal radiologic alterations are often subtle and easy to overlook yet become readily identified on subsequent examinations. Observers may differ in evaluating a segment as normal or minimally diseased. This circumstance may be responsible for reports of the "spread" of granulomatous disease into an apparently normal segment of bowel; in other words, it may represent a worsening of a mild inflammatory process rather than the advent of disease in a previously uninvolved area. It is well known that recurrence of granulomatous disease in the colon or small bowel may develop following surgery (14) Linear extension of disease in the absence of surgery however, is uncommon in our experience, although it does occur. Normal areas between skip lesions may become severely and diffusely ulcerated in a short period of time.

Reversibility

Marked reversibility may be observed in serial examinations of patients with granulomatous disease (15). This change has usually followed a course of therapy with steroids or sometimes antibiotics (16) in a patient with active, acute disease. We have noted dramatic instances of this type of radiologic recovery. The marked submucosal edema may disappear, providing an appearance indistinguishable from that of a normal colon. Unlike ulcerative colitis, in which occasionally even the chronic changes of a shortened colon may return to normal resolution in the more chronic cases of granulomatous colitis has not been observed.

Inflammatory Disease of the Stoma

Because ileostomy and colectomy are performed for both ulcerative and granulomatous colitis, the appearance of postoperative inflammatory disease of the ileum proximal to the stoma is important. Such "prestomal ileitis" is of two varieties. One is secondary to obstruction to the stoma, a mechanical problem related to narrowing or retraction of the ileostomy. This abnormality is termed ileostomy dysfunction. The other variety of prestomal ileitis is due to extension of granulomatous disease. Ileostomy dysfunction may be seen following surgery for both ulcerative and granulomatous colitis and is related to construction of the ileostomy and to local mechanical complications. Development of the granulomatous process in the region of the stoma is seen only if surgery was performed for granulomatous disease. In our own series of cases, prestomal granulomatous ileitis has been seen with increasing frequency in patients with preoperative disease in both the ileum and colon. We have seen this complication less commonly in those patients in whom the preoperative disease has been confined to the colon.

The radiologic findings in ileostomy dysfunction and granulomatous prestomal ileitis differ. In ileostomy dysfunction, the ileum is dilated and there are abundant secretions. The folds are slightly thickened and ulcerations are minimal and difficult to identify. When prestomal granulomatous ileitis develops, however, the radiologic findings are identical to those of regional enteritis (Fig. 20).

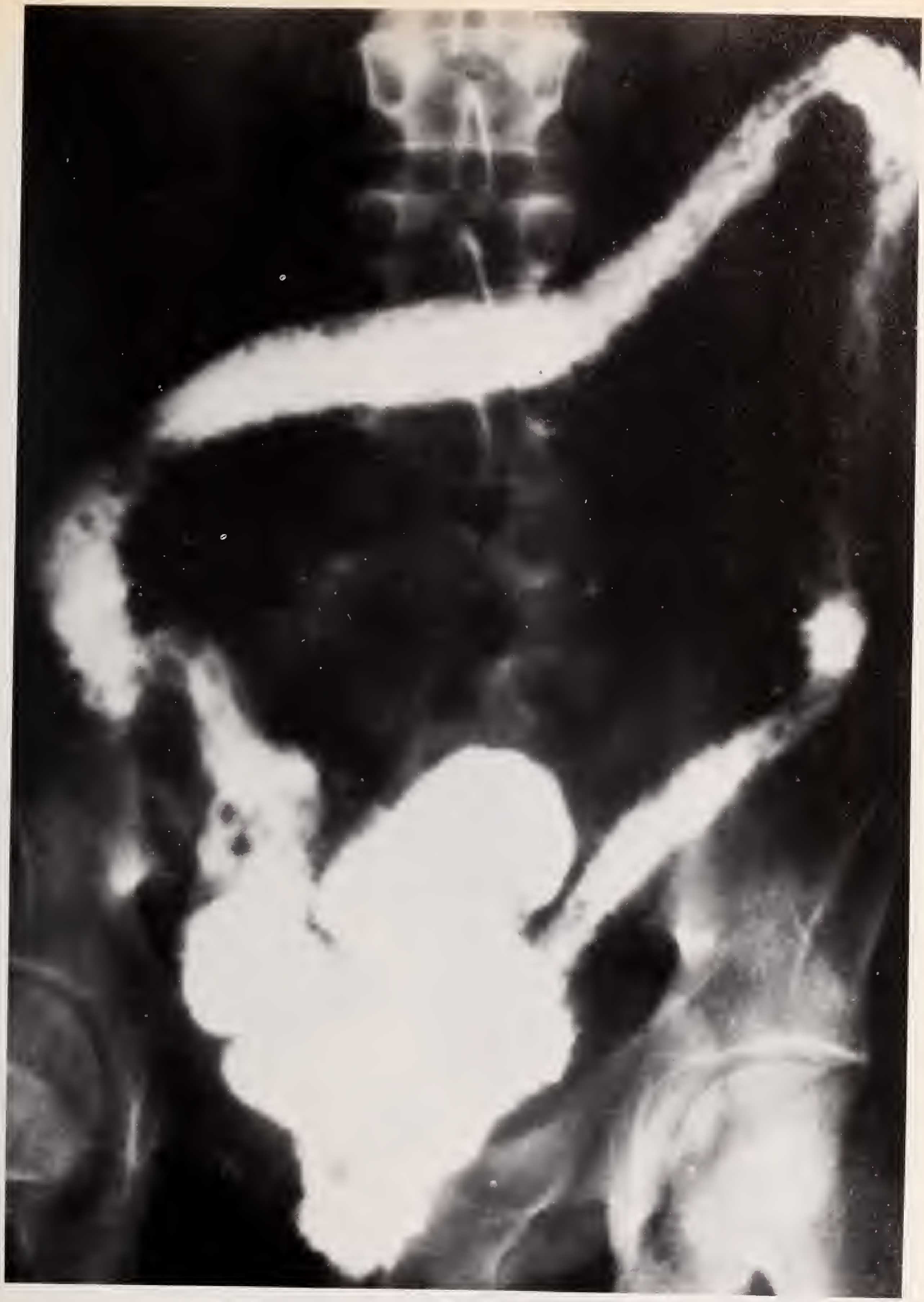


FIG. 14. Granulomatous ileocolitis. There is a moderate degree of narrowing and rigidity of the entire colon, ulcerations of the mucosa and numerous small inflammatory polyps. This type of diffuse involvement is more commonly seen in ulcerative colitis but it can also be identified in granulomatous disease. The involvement of the terminal ileum in this case with typical regional enteritis enables the radiologist to make a diagnosis of granulomatous ileocolitis.

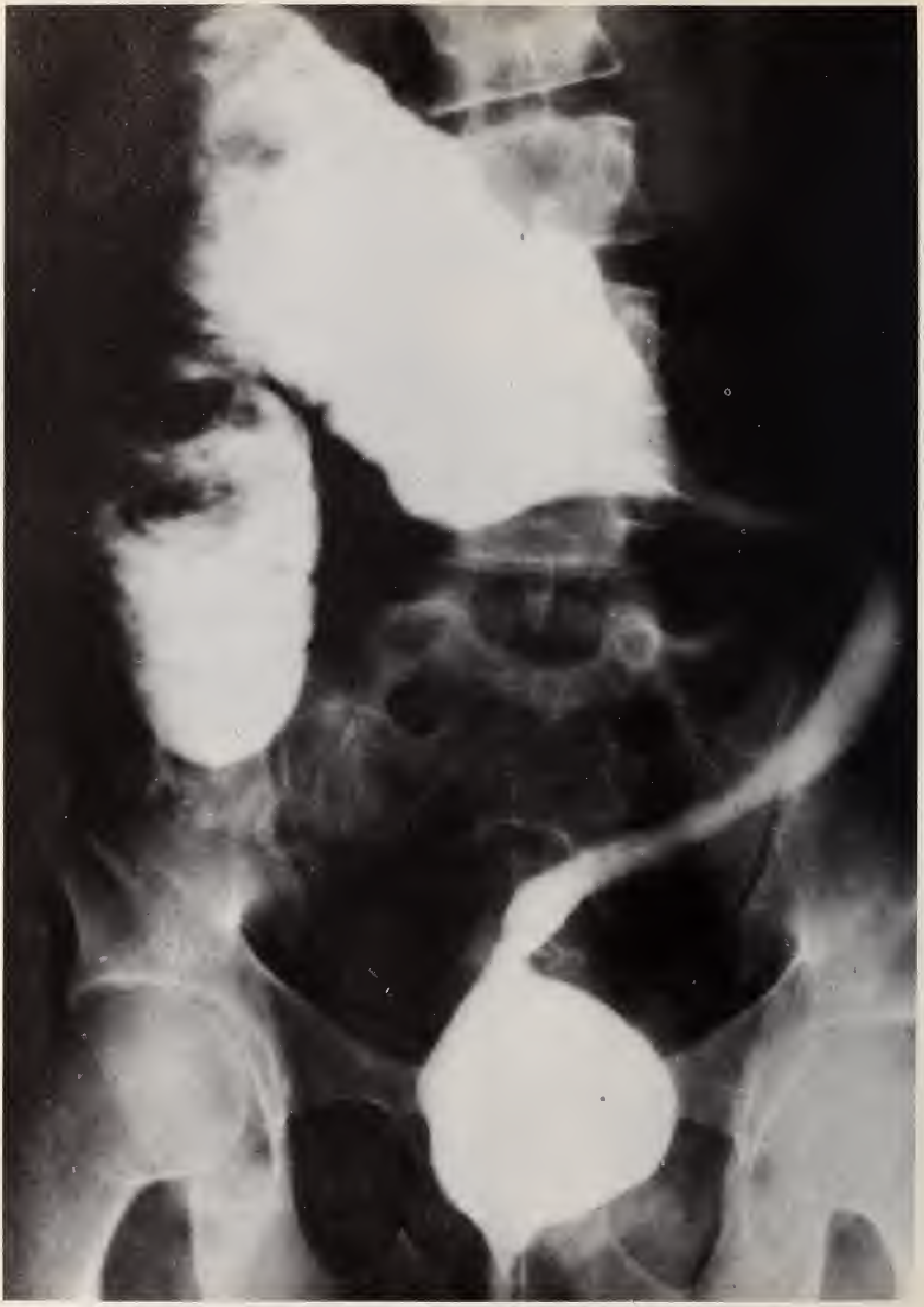


FIG. 15. Granulomatous colitis. There is predominantly left sided involvement in association with shortening, narrowing, and stricture of th descending colon, sigmoid and rectum. Note that the splenic flexure has been markedly depressed.

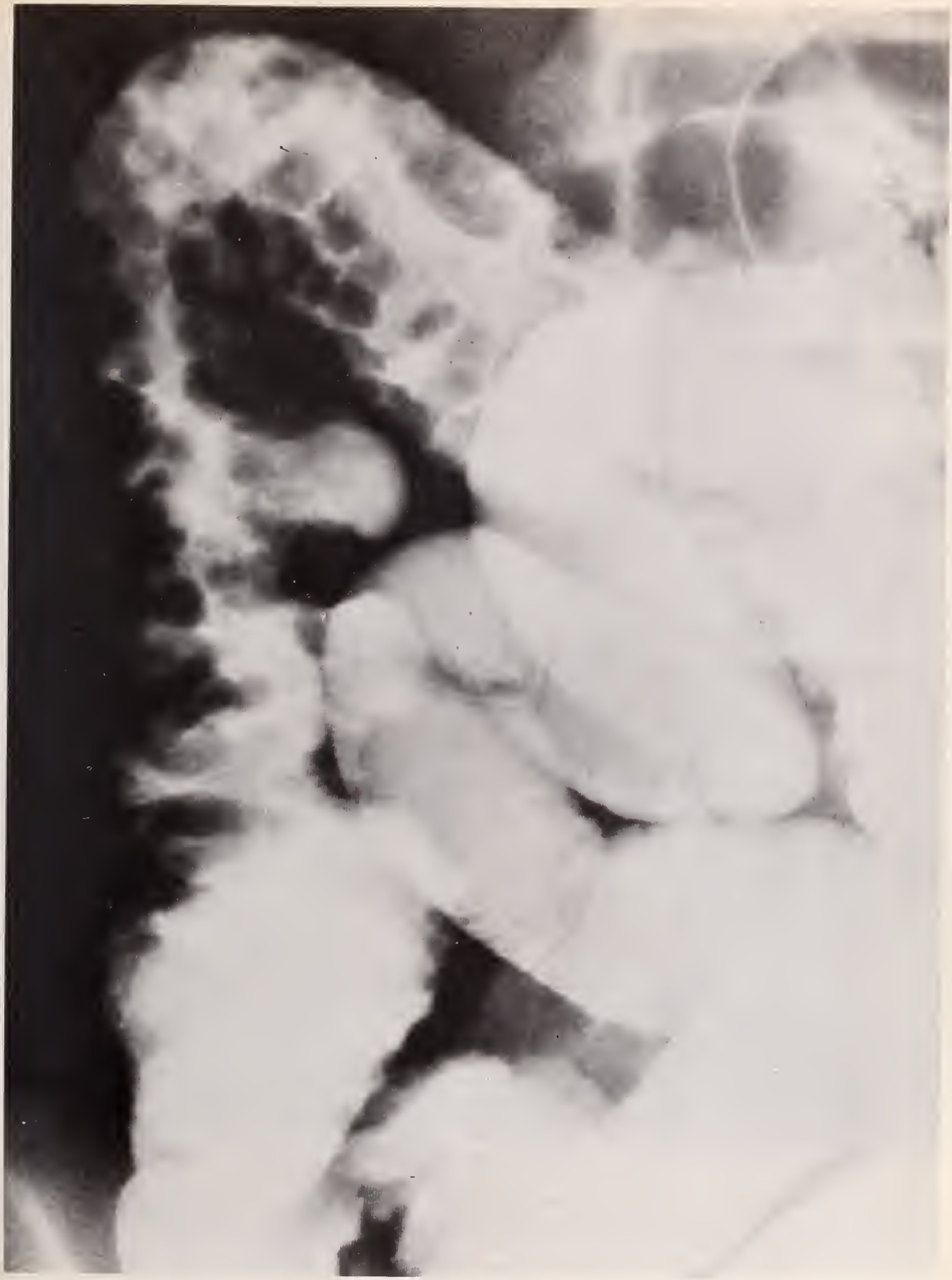


FIG. 16. Granulomatous colitis. Spot film of the right side of the colon demonstrating transverse and linear ulcerations, large inflammatory polyps, narrowing, rigidity and irregular contours.

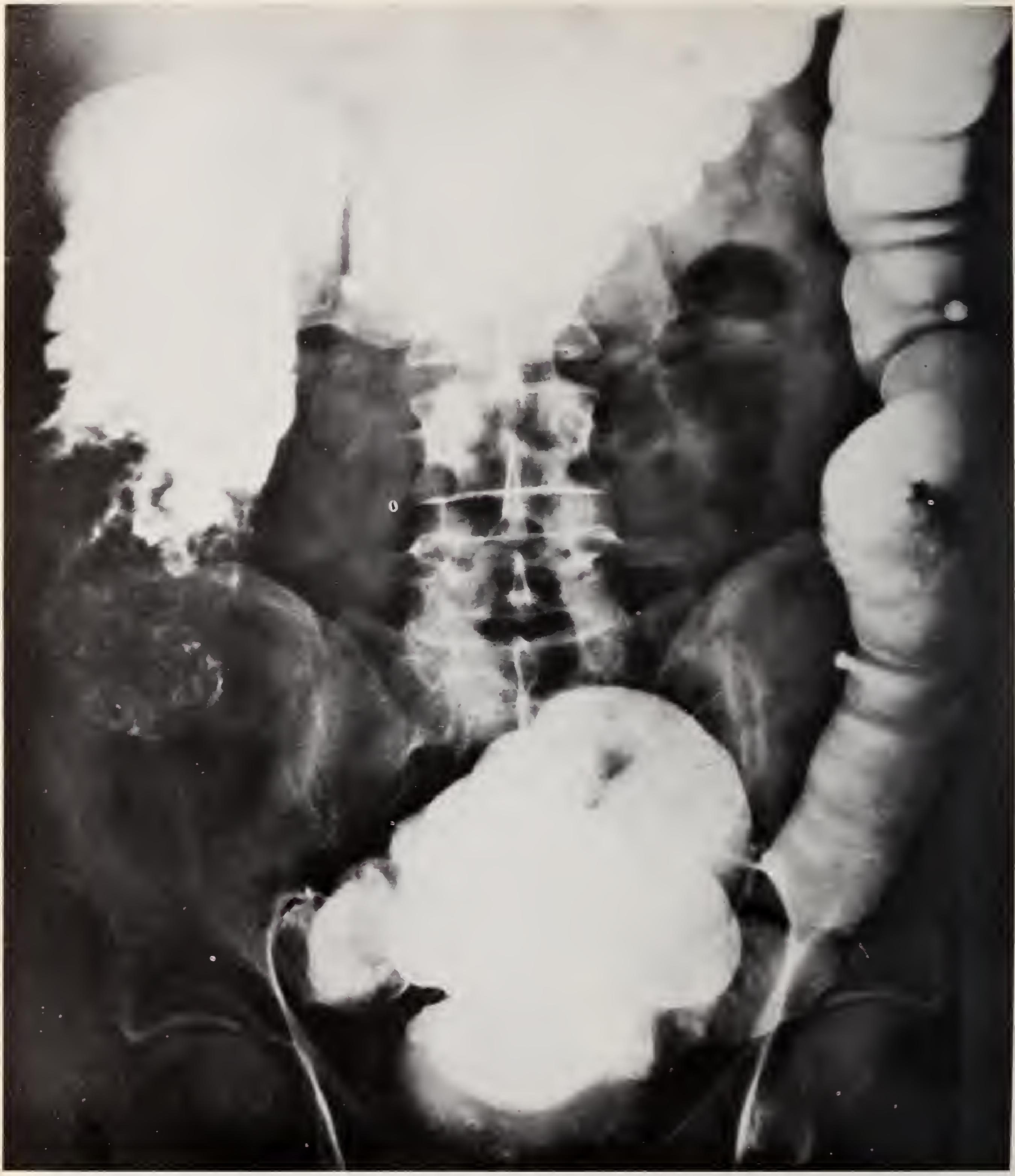


Fig. 17a. Granulomatous colitis. Massed inflammatory polyps in the right side of the colon.

Crohn's Disease of the Colon and Diverticulitis

Diverticulitis may be confused with granulomatous colitis, especially when granulomatous disease is confined to the sigmoid. Granulomatous colitis can occur in middle-aged and elderly patients, an age group in which diverticulosis and diverticulitis are also often found. The two diseases, therefore, may coexist.

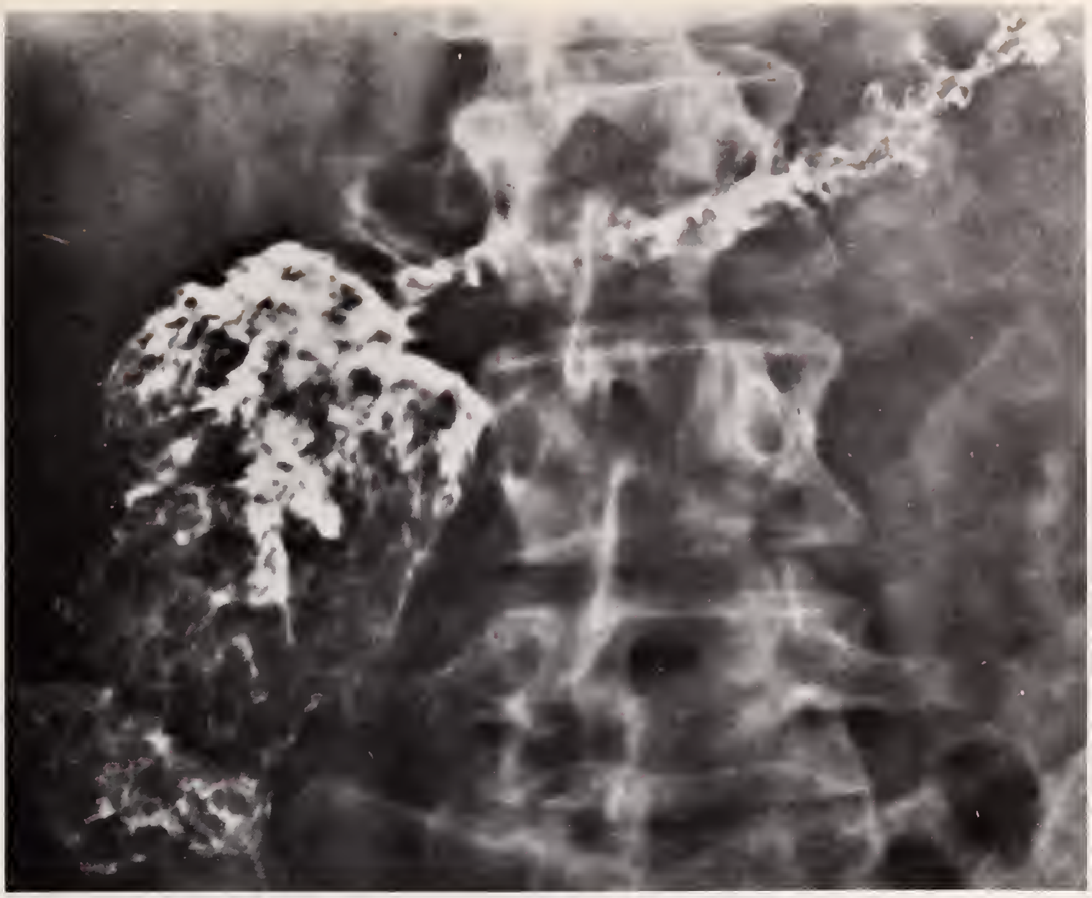
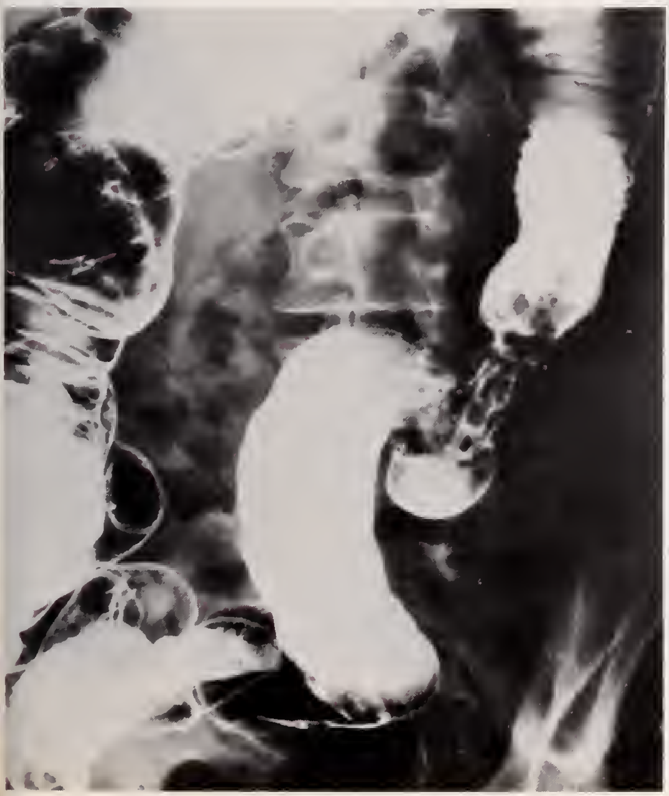


FIG. 17b. Same patient as Fig. 17a. Evacuation film again demonstrating massed polyps. This should not be confused with a carcinoma.



In Crohn's disease of the colon the involved segment tends to be long–usually 10 cm or longer–whereas in diverticulitis the segment is often short, perhaps 3 to 6 cm in length. However, the involved segment in diverticulitis can become more extensive (17). A tract longer than 10 cm may be observed due to multiple perforations of diverticula or to communicating diverticulitis.

When granulomatous colitis develops in a patient with diverticula, the transverse fissures penetrate easily through the mucosa of the diverticulum producing diverticulitis (18). The abscesses of granulomatous colitis often have a triangular shape but at times they may be difficult to distinguish from coexistent diverticula. In granulomatous colitis, a cobblestone appearance is frequently seen; in a perforated diverticulum, the abscess usually creates an extramural defect or an arcuate configuration of the folds which stretch over the abscess. The transverse fissures and marked mucosal edema of granulomatous colitis help to distinguish this entry from diverticulitis.

FIG. 17c. Granulomatous colitis. Partial stricture in the region of the distal descending colon in association with large inflammatory polyps and pseudodiverticulum. The small bowel was also involved in this case.

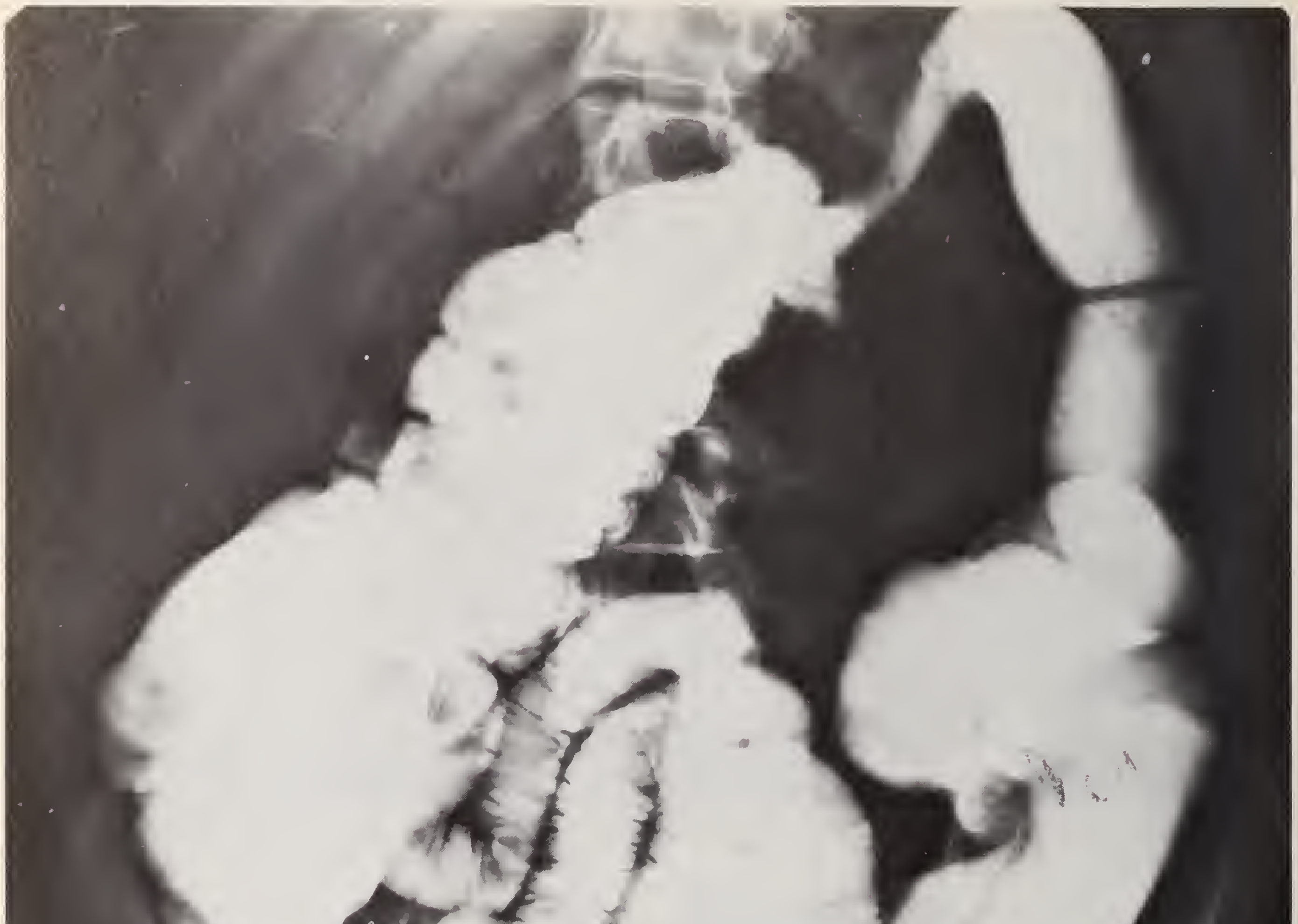


FIG. 18. Granulomatous colitis. There are strictures involving the distal transverse colon and the distal descending colon, in association with pseudodiverticula. In the absence of a lesion in the descending colon the diagnosis of granulomatous colitis would be uncertain.

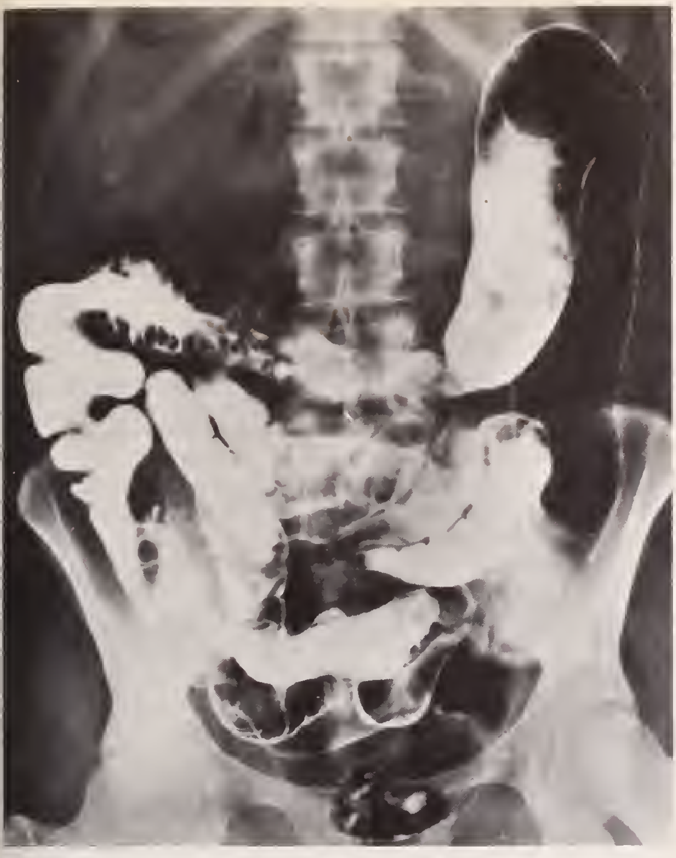


FIG. 19. Granulomatous ileocolitis. The ileum and right side of the colon are involved. Transverse ulcerations and inflammatory polyps are seen in the proximal transverse colon. A small fistulous communication from the ileum to the cecum is noted. The left side of the colon is normal.

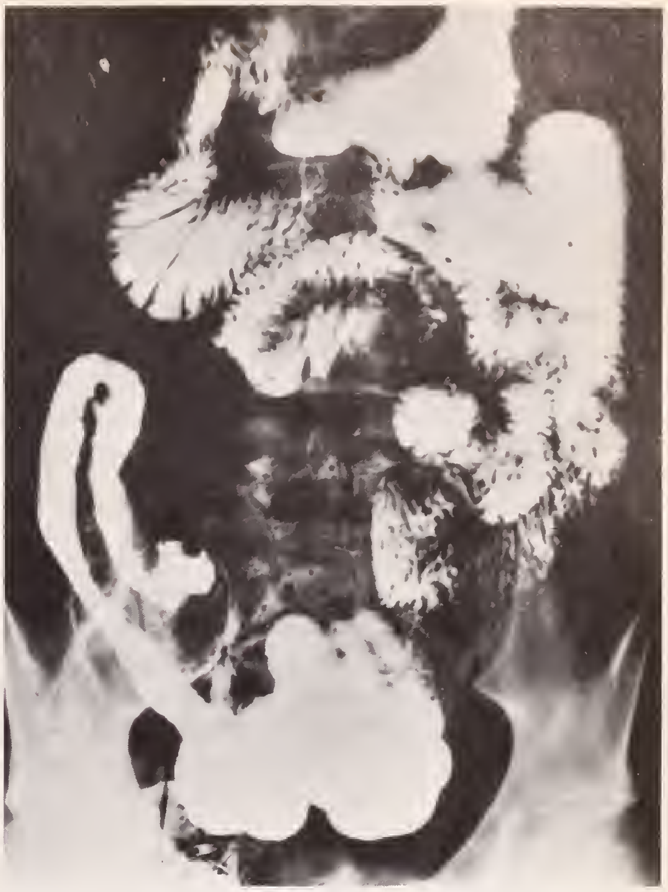


FIG. 20. Recurrent granulomatous disease at the ileostomy site following resection of the colon for granulomatous colitis. There is recurrent ileitis involving the distal 12–18 inches of ileum proximal to the stoma characterized by narrowing, rigidity and ulceration of the mucosa.

Angiography in Granulomatous Disease

With the advent of angiographic techniques for the examination of the vasculature of the large and small bowel, it was hoped that a means had been found to elucidate a possible vascular etiology for granulomatous disease or at least to provide another way to distinguish ulcerative and Crohn's colitis.

Some angiographers have found ischemic changes in angiograms of the colon in granulomatous disease (19) and others (20) have described narrowing of the arterial walls.

Arterial injection techniques have been employed in resected specimens of bowel to compare the radiologic appearances of small vessels in the wall of the intestine with large histologic sections of the same area. Changes were found that varied with the severity of the inflammatory reaction and included increased vascularity, a distribution of the vessels consistent with transmural thickening of the wall, and a close relationship between ulcers and the vessels such that ulcers were found to develop at the point of entrance of arteries through the muscularis. Inflammation tended to follow vascular or lymphatic pathways. Arterial occlusion was rarely seen. Vascular changes were difficult to identify or were absent in specimens with only mild inflammation.

In specimens of ulcerative colitis studied by the same technique, hypervascularity was more evident than in granulomatous disease but for the most part was confined—as in the pathological process—to the mucosa and submucosa. In inactive or "burnt-out" colitis, vascularity was not increased and changes in arteries were minimal.

It is our impression that, at this time, angiographic techniques are of little help in the differential diagnosis of ulcerative and Crohn's colitis and offer no insight into the etiologies of these diseases. The reported changes in blood vessels seem to be predictable and to parallel the distribution and the degree of inflammation. As new angiographic methods are developed, perhaps other and more significant information will be acquired about the vascular changes associated with inflammatory bowel disease.

Differential Diagnosis of Crohn's Disease of the Colon

Amebiasis

In the acute stage, amebiasis resembles ulcerative colitis. In chronic disease, especially when the rectum is spared, it may simulate granulomatous colitis (21). Specific features of granulomatous disease such as cobblestoning, strictures or fistulas are uncommon. In milder cases, with distortion of the haustral markings, narrowing and rigidity, differentiation is difficult. The small bowel is not usually involved in amebiasis. The so-called "cone-shaped cecum" sometimes decribed in amebiasis may occur in any right lower quadrant inflammatory process and is not diagnostic.

Tuberculosis

It is impossible to differentiate tuberculosis from Crohn's ileocolitis. In those instances in which the inflammatory process is confined to the distal ileum and proximal colon, tuberculosis must be considered. Cases of intestinal tuberculosis may be associated with a normal chest x-ray.

Ischemic Colitis

Ischemic colitis is easily differentiated from granulomatous colitis by the characteristic acute episode of abdominal pain and bleeding, and by the rapid progression of radiologic findings from a stage of inflammatory edema, with thumbprinting, segmental disease, spasm, irritability and increased secretions, to resolution or stenosis. The sequence of events rarely requires more than six weeks. If the patient is examined radiologically at any particular phase of this process, the appearance may suggest inflammatory disease. Pseudosacculations are common residua of ischemic disease.

Scirrhous Carcinoma of the Colon

Long segments of colon, usually sigmoid, may be involved with carcinoma in a linitis plastica or scirrhous presentation. The differential diagnosis from a single segment of granulomatous colitis may be difficult. In carcinoma, however, nodularity is prominent and the inflammatory mucosal alterations of granulomatous colitis are not usually seen.

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Cholinomimetic Treatment of Neuropsychiatric Disorders: A Review of Recent Developments*

KENNETH L. DAVIS, M.D.

Cholinergic imbalance in the central nervous system has been implicated in a number of neuropsychiatric disorders including mania, depression, schizophrenia, Huntington's disease, tardive dyskinesia and senile dementia (1–3). Recently, attempts have been made to treat these disorders with physostigmine, arecoline, choline chloride and dimethylaminoethanol. This paper will briefly review the clinical evidence suggesting that pharmacologic alterations of cholinergic activity is a viable strategy for the treatment of some neuropsychiatric patients. A more extensive review of the preclinical data supporting the relative cholinergic imbalance hypothesis of psychoses has been published already (2).

Psychoses

The possibility that increasing cholinergic activity in the central nervous system could diminish manic symptoms was suggested over 25 years ago (4). This approach to the treatment of mania received little attention until 20 years later, after the report of a double-blind controlled study of the effects of physostigmine on eight manic patients. In this study, physostigmine rapidly suppressed manic symptoms in all patients, but neostigmine, which does not cross the blood-brain barrier, was without effect (5). Subsequently, it was argued that the action of physostigmine in mania was a manifestation of the anergic syndrome it produced and did not reflect a true change in mood and thought content (6, 7). However, simultaneous administration of physostigmine and an antiemetic established that the drug changed manic mood and thought content without producing an anergic syndrome in euphoric manic patients (8).

The clinical utility of this finding rests on the development of a safe, long-acting cholinomimetic. Choline may be such an agent since the chemical is believed to increase brain levels of acetylcholine, and increase central cholinergic activity (9–14). To date, one manic patient has completed a trial of choline chloride. That patient had fewer symptoms of mania during choline chloride administration than during either the baseline or placebo periods (15). Additional trials are underway.

A cholinergic involvement in depression is also suggested by a number of studies. Both psychiatric patients and normal subjects have been reported to become clinically depressed after exposure to irreversible organophosphate inhibitors (4, 16–17). Physostimine has been found to produce sadness, apathy and even suicidal ideation in normal subjects who were daily marijuana users, or who had a past history of depression (7, 18, 19). However, the development of a depressive syndrome in patients with other psychiatric diagnoses or normal subjects following physostigmine administration has not been uniformly observed (7, 20, 21). The administration of choline chloride to patients with tardive dyskinesia has been associated with severe depression that was reversible by atropine (22). These observations are all consistent with the possibility that part of the antidepressant action of the tricyclics is related to their anticholinergic properties.

In contrast to mania, there is no convincing evidence that cholinomimetics diminish schizophrenic symptoms (15, 21, 23–26). Almost all of the studies that have investigated the effect of increased central cholinergic activity upon schizophrenic symptoms have administered a relatively short-acting cholinergic agent for a brief period of treatment. These experimental paradigms have not maximized the likelihood of demonstrating a therapeutic efficacy for cholinomimetics in schizophrenia. An extended duration of administration may be required for a

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From the Psychiatric Clinical Research Center, Veterans Administration Hospital, Palo Alto, CA. and Stanford University School of Medicine, Stanford, CA.

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cholinomimetic to have a beneficial effect. Furthermore, the effects of a drug on schizophrenic symptoms can be exceedingly difficult to evaluate when the drug has a half-life as brief as physostigmine, and side effects including nausea, vomiting and confusion. Obviously, a long-acting central cholinomimetic with few side effects would facilitate further investigation.

Dimethylaminoethanol (Deanol) presumed to be a precursor of choline and acetylcholine (52), has been administered chronically to schizophrenic patients (27–28). Although these reports were mildly favorable, they did not establish Deanol unequivocably as an antipsychotic agent. The influence of Deanol in increasing brain acetylcholine is in doubt (10, 29–32). On the other hand, the evidence that choline increases brain acetylcholine levels, and central cholinergic activity is more uncertain (9–14, 33). Consequently, a recently concluded trial of choline chloride in eight schizophrenic patients was an important test of agents that increase central cholinergic activity to influence the symptoms of schizophrenia (15, 34). Choline was administered in a single blind, cross-over study for three weeks (34). The results did not suggest a beneficial effect of choline in schizophrenia, but there was a significant trend for patients to have higher depression scores while receiving choline than during either baseline or placebo periods. This result is consistent with the hypothesis that increased cholinergic activity underlines some depressive syndromes.

The possibility that cholinergic agents may have a role in the treatment of schizophrenia would be strengthened if anticholinergic drugs worsened schizophrenic symptoms. A potent anticholinergic agent, Ditran, has been administered to a number of schizophrenic patients (35). Although Ditran aggravated schizophrenic symptoms, EEG data indicated that this effect was a function of the general deliriant producing properties of the drug and not a specific action on schizophrenic process. It has been claimed that concomitant administration of anticholinergic, anti-Parkinsonian agents decreases the efficacy of neuroleptic drugs (36). This interesting possibility will require additional investigation before it can be fully accepted. Conceivably, the effect is related to the ability of anticholinergic drugs to reduce steady state levels of chlorpromazine (37).

The basis for the cholinomimetic treatment of schizophrenia is the assumption that cholinergic-dopaminergic interactions in the mesolimbic system are similar to cholinergic-dopaminergic interactions in the basal ganglia. Stereotypy in rodents is a function of augmented nigrostriatal dopaminergic activity (38, 39). Centrally acting cholinomimetics suppress the stereotypic behavior induced by amphetamine or apomorphine (13, 40–42).

Increased dopaminergic activity in the mesolimbic area of the brain is associated with marked locomotor activity (43–46). If cholinomimetics have the same effect on dopamine related behaviors in the mesolimbic system as they do in the nigrostriatal tract, these drugs should suppress dopamine induced locomotor activity. The opposite effect has been reported. Carbachol, like dopamine, increased locomotor activity when injected into the nucleus accumbens (45). In contrast, most antipsychotic agents suppress dopamine induced locomotor activity with a potency that correlates with their antipsychotic activity (46). Thus if decreasing mesolimbic dopamine associated behaviors is intrinsic to their antipsychotic activity, centrally active cholinomimetics do not display this quality.

Movement Disorders

Pharmacologic studies have indicated that patients with tardive dyskinesia may have a relative predominance of dopaminergic transmission and cholinergic underactivity in the basal ganglia (47–49). Thus it has been shown that physostigmine can decrease the frequency and severity of the abnormal involuntary movements of patients with tardive dyskinesia (47, 48, 50, 51). The general applicability of the actions of physostigmine to alleviate the symptoms of tardive dyskinesia requires the availability of a safe, long-acting cholinomimetic. Deanol has been administered without a significant clinical effect in a number of double-blind protocols (53–56).

Rather large doses of choline chloride have been used successfully in patients with tardive dyskinesia. The first double-blind controlled study indicating the positive effects of choline chloride in this disorder has subsequently been confirmed by a number of groups (50, 56–68). These results are the first verified treatment for patients with irreversible tardive dyskinesia. However, a number of factors should be noted. Although choline does yield a statistically significant improvement in the symptoms of tardive dyskinesia, some degree of abnormal movement persists and some patients are reported to be unimproved (50, 56, 57). Furthermore, if augmentation in cholinergic activity has an inhibitory effect on dopaminergic impulse flow in the nigrostriatal tract, the long-term use of cholinomimetics could worsen the symptoms of tardive dyskinesia upon discontinuation of cholinomimetic treatment.

Autopsy material derived from the brains of patients with Huntington's disease demonstrate a substantial loss in choline acetyltransferase and glutamic acid decarboxylase activity in the neostriatum (59). These enzymes changes are presumed to reflect a loss in cholinergic and GABA-minergic neurons. Pharmacologic investigations of patients with Huntington's disease indicate that agents decreasing dopaminergic activity or increasing cholinergic activity can diminish the frequency of choreiform movements of patients with this degenerative disorder (50, 60–63). Taken together these anatomic and pharmacologic studies suggest a relative cholinergic and GA-

BAminergic underactivity and dopaminergic overactivity in the basal ganglia of patients with Huntington's disease.

All patients with Huntington's disease have not responded favorably to the administration of cholinomimetics and some have been unaffected (50, 62, 64). Ligand binding studies of neurons from the neostriatum of patients with Huntington's disease demonstrate diminished muscarinic receptor density (59). Thus, some patients with Huntington's disease may have insufficient postsynaptic muscarinic receptors to allow an acetylcholinesterase inhibitor to increase central cholinergic neurotransmission, and diminish choreiform movements.

Trials with choline chloride in patients with Huntington's disease confirm this possibility. A number of investigators have not found that choline chloride consistently improved the abnormal involuntary movements of patients with Huntington's disease (50, 58, 65, 66). Those patients who were improved by choline chloride were previously benefited by an intravenous infusion of physostigmine (50). There was a perfect correlation between the response to physostigmine and the response to choline chloride. These data suggest that a subgroup of patients with Huntington's disease may have the frequency of their abnormal involuntary movements diminished by the administration of cholinomimetics. Presumably these patients do not have an extensive loss of postsynaptic muscarinic receptors. Additional work will be required to confirm this possibility, and to determine the clinical correlates that might identify patients with Huntington's disease who are cholinomimetic responders.

Memory Disturbances

Brain material obtained at autopsy from patients with Alzheimer's type of senile dementia have demonstrated a marked loss of choline acetyltransferase (CAT) activity. Enzyme changes have been localized in the caudate, amygdala, hippocampus and cortex (67–69). Changes in the activity of other enzymes involved in neurotransmitter synthesis were not found in the brain areas having the greatest changes in CAT activity (68). These studies suggest a degeneration of cholinergic neurons, and a loss in cholinergic activity in patients with Alzheimer's disease.

Human and animal studies confirm the relationship between memory and central cholinergic activity. Blockade of central muscarinic receptors profoundly impairs long-term memory (LTM) processes in man (70–79). On the other hand, a relatively low dose of physostigmine (.8 mg) markedly enhanced the ability of a woman with the sequela of herpes simplex encephalitis to acquire new information into LTM (80). In a double-blind cross-over study, 19 normal subjects displayed a significant improvement on various LTM tasks during an infusion of a low dose of physostigmine (81). Similar results have been obtained with the cholinomimetic drug arecoline (82).

As was the situation for other neuropsychiatric disorders benefited by physostigmine, the clinical usefulness of these results is a function of the availability of a long-acting, safe cholinomimetic. A number of trials have been carried out investigating the effects of choline on memory (83–85). These studies indicate that there is a very subtle relationship between the dose of choline and its effect on LTM. Improvement may occur at relatively low doses (8–10 gm/day), whereas higher doses (16–20 gm/day) do not yield positive results. Thus the relationship between choline dose and LTM may resemble an inverted U-shaped curve. A similar curvilinear relationship has been reported for the effect of physostigmine upon memory (7).

Clinical and neurochemical studies clearly suggest that central cholinomimetic agents should be tested in elderly people with age-related memory losses and in patients with senile dementia. Should increasing central cholinergic activity prove a viable treatment strategy for patients with Alzheimer's disease, its efficacy may be a function of the extent that cholinergic neurons and postsynaptic cholinergic receptors are degenerated.

Summary

The investigation of cholinergic mechanisms in affective disorders, schizophrenia, tardive dyskinesia, Huntington's disease and Alzheimer's disease has brought about a new way to consider these conditions. To the extent that central cholinergic underactivity contributes to these disorders, drugs that increase central cholinergic activity may produce favorable clinical effects. The development of long-acting central cholinergic agents will be eagerly awaited for their potential clinical utility.

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Thyroid Nodules in Children: A Ten Year Experience at One Institution

SAMUEL H. SILVERMAN, M.D. MOSES NUSSBAUM, M.D.* AND AARON R. RAUSEN, M.D.

Abstract

Seventeen pediatric patients with thyroid nodules were treated surgically at Beth Israel Medical Center in New York over a ten-year period. Five of 14 patients with solitary nodules had a malignancy. None of the three patients with multiple nodules had malignancy. There was no history of prior radiation in any of the patients. There was no microscopic evidence of thyroiditis. The high incidence of malignancy in children with thyroid nodules and the inconclusive information obtained from history and laboratory data suggest that surgery be done on all children with thyroid nodules.

Seventeen children with surgically treated thyroid nodules were seen between 1966 and 1975 at Beth Israel Medical Center. Their histories, physical findings, thyroid function tests, isotopic and pathologic studies form the basis of this report.

Materials and Methods

All patients were identified by a review of the professional activity study (PAS) program records of Beth Israel Medical Center. Specific patient data were compiled from records as well as by followup with the private physician. Histologic sections were reviewed to verify the diagnosis and to rule out thyroiditis.

Results

Twelve of the 17 patients had benign nodules; five had malignant nodules (Tables I, II). All patients were female except one with a benign nodule and one with a malignant nodule. The age range was seven to 18 years with a mean of 15 years. Only two patients were prepubescent.

All 17 patients were asymptomatic and euthyroid. No history of prior irradiation or ingestion of goitrogens was elicited. Four of the benign nodules and one of the malignant nodules were increasing in size prior to surgery.

Five patients, of whom four were female, had carcinoma of the thyroid. Two had papillary carcinomas and three had mixed follicular-papillary carcinoma. None of the seventeen patients had any histologic evidence of thyroiditis on a retrospective review of all surgical material.

Three patients were placed on thyroid hormone medication for periods of three to nine months prior to surgery without significant effect on the size of their nodules; two of these patients had malignancies. Fourteen patients had a single thyroid nodule and three had multiple nodules. There was no evidence of malignancy in any patient with multiple nodules. The size of the nodules ranged from 1.5 cm to 4 cm in diameter. Consistency of the nodule was of no diagnostic help in distinguishing benign from malignant lesions. Three of the patients with carcinoma and none with benign lesions had cervical nodes greater than 1.5 cm at the time of hospitalization for surgery.

A variety of thyroid function studies were normal. Three of the five patients with thyroid malignancy were studied with radioactive iodine uptake scans and all had cold nodules. Of ten patients with benign nodules who were studied with radioactive iodine uptake scans, eight had cold nodules.

No operative mortality occurred. M.Z. had surgical hypoparathyroidism; H.L. developed immediate postoperative respiratory failure of unknown cause and recovered completely after supportive treatment.

The five patients with carcinoma have been followed three to 12 years. Four have been free of disease since the original surgery. R.L. has undergone contralateral radical neck dissection and two courses of therapeutic radioactive iodine. She is presently asymptomatic and free of disease.

From the Departments of Pediatrics and *Surgery, Beth Israel Medical Center, and Mount Sinai School of Medicine (CUNY), New York, N.Y.

Requests for reprints should be sent to Dr. Samuel H. Silverman, 135 Rector Street, Perth Amboy, N.J. 08861.

TABLE I

Patients with Benign Thyroid Nodules

Patient	Age	Sex	Year of Operation	Clinical Data	Thyroid Scan	Pathology	Surgery
R.R.	7	F	1974	3 mo history rightsided nodule 1.5 × 1.5 cm	—	Hemorrhagic cyst	Excision of cyst
H.C.	9	F	1976	Routine examination Isthmus nodule 1.5 × 1.5 cm	Cold	Colloid nodule	Isthmusectomy
A.M.	14	F	1973	1 yr history left thyroid nodule 4 × 3 cm	Cold	Colloid adenoma	Left hemithyroidectomy
L.S.	14	F	1974	2 mo history right multinodular thyroid 3 × 2 cm	Cold	Multinodular adenoma	Right hemithyroidectomy
R.L.	14	F	1972	Routine examination Right thyroid nodule 3 × 2 cm	—	Embryonal adenoma	Right hemithyroidectomy
M.B.	15	M	1975	3 mo history left thyroid nodule 5 × 3 cm	Cold	Adenoma with degenerative changes	Left hemithyroidectomy
S.W.	15	F	1969	3 mo history left thyroid nodule 2 × 2 cm	Cold	Follicular adenoma	Left hemithyroidectomy and isthmusectomy
E.K.	16	F	1974	1 yr history treated with thyroid extract for 7 mos. Right thyroid nodule 1.5 × 1.5 cm	Normal	Adenoma with cystic degeneration	Isthmusectomy
H.L.	16	F	1976	3 mo history left thyroid nodule 3 × 3 cm	Hot	Micro and macro follicular adenoma	Left hemithyroidectomy
J.B.	17	F	1972	5 mo history right thyroid nodule 2 × 2 cm	Cold	Multinodular follicular adenoma with cystic degeneration	Right hemithyroidectomy. Wedge resection left lower lobe of thyroid
R.M.	18	F	1968	2 yr history bilateral nodules 4 × 4 cm	—	Papillary follicular adenoma with cystic degeneration	Excision of cysts
A.R.	18	F	1970	2 mo history left thyroid nodule 2 × 2 cm	Cold	Follicular adenoma	Left hemithyroidectomy

TABLE II

Patients with Malignant Thyroid Nodules

Patient	Age	Sex	Year of Operation	Clinical Data	Thyroid Scan	Pathology	Surgery
R.F.	14	M	1975	Routine examination Thyroid nodule 4 × 3 cm. Right	Cold	Mixed follicular papillary carcinoma; follicular predominant	Right lobe thyroid removed. Left lobe subtotal resection. Lymph nodes removed.
R.L.	14	F	1966	Thyroid nodules Cervical node (small)	—	Papillary carcinoma	Complete thyroidectomy. Modified neck resection
F.Q.	15	F	1970	Cervical adenopathy 1½ × 1½ cm for one year. Retrospectively thyroid nodule 1.5 × 3 cm	—	Follicular papillary carcinoma	Total thyroidectomy. Radical right neck resection
M.Z.	17	F	1973	Treated with thyroid extract for 8 mos. Thyroid nodule 5 × 6 cm Cervical lymphadenopathy	Cold	Papillary carcinoma	Total thyroidectomy. Radical neck resection. Superior mediastinal dissection. Parathyroid glands inadvertently removed.
J.P.	18	F	1970	Treated with Cytomel for 3 mos. Right thyroid nodule 2 × 1 cm	Cold	Mixed follicular papillary carcinoma	Thymectomy. Right lobe thyroid removed. Left lobe subtotal resection. Lymph node removed.

Discussion

Thyroid carcinoma frequently metastasizes before the malignancy is diagnosed. A papillary component in thyroid carcinoma is the most common form of malignancy. This tumor is usually slow growing and its course, with or without intervention, may be measured in decades. In occasional patients, papillary carcinoma is lethal (1, 2) and may progress in its later stages to a more anaplastic form (3, 4).

In this series, the size, consistency and rate of growth of the thyroid nodules did not help in distinguishing benign from malignant lesions. Three of our five patients with malignancies had significant cervical adenopathy. Other indications for immediate thyroid surgery, in which the yield of carcinoma may be great, include recurrent laryngeal nerve dysfunction, pressure of the thyroid on surrounding structures, and attachment of a nodule to overlying tissue.

The theoretical basis for utilizing radioactive iodine, americium, and combinations of isotope scans in differentiating a carcinoma from a benign lesion is based on the observation that the malignant tissues usually do not readily metabolize the isotope (5–7). In benign lesions, metabolism and consequent affinity for the isotope have been said to be normal (5). Unfortunately, this is not the situation since some benign lesions are nonfunctional cysts and the use of radioisotope studies may, therefore, be confusing. In this series, eight of ten patients with benign lesions studied had cold nodules. This is consistent with other series. Newer modes of scanning have decreased the number of false positive scans. However, a number of benign lesions still have cold areas (6). In addition, a number of carcinomas associated with hyperfunctioning nodules have been reported (5, 8, 9). Thus, a firm diagnosis of a malignant nodule cannot be made with isotope studies alone.

Thyroid function studies also do not separate a benign from a malignant lesion. However, biochemical and isotope studies are important to define thyroid functional status as well as the presence of agenesis of the thyroid, aberrant tissue or thyroiditis. Thyroiditis requires careful, ongoing observation since carcinoma in such an involved gland has been reported (10).

Reports concerning the incidence of malignancy in thyroid nodules deal predominantly with adults. Thyroid nodules are rare in children, particularly the prepubescent child. The incidence of malignancy in children who are operated on for thyroid nodules has a wide range of from 20 to 73% (Table III) (11–17). This is greater than the 0 to 8% incidence for thyroid malignancy found at surgery in adults with nodules (18, 19).

Advocacy of observation as opposed to surgery for thyroid nodules continues to wane. With the high incidence of malignancy in thyroid nodules in children as opposed to adults, and in view of the inability to make a definitive diagnosis of malignancy by clinical and laboratory examination alone, extirpative surgical intervention appears to be the treatment of choice in all children with thyroid nodules.

TABLE III

Literature Review of Surgically Treated Thyroid Nodules Excluding Thyroiditis and Congenital Anomalies

Reference	Total Pediatric Surgical Patients with Thyroid Nodules	Malignant Thyroid Nodules	Percent of Malignancy
M. B. Scott, et al[11]	27	6	22
R. C. Horn, et al[12]	15	11	73
R. Ward[13]			
0–15 yrs			47
0–21 yrs			32
W. J. Norris, et al[14]	14	4	28
H. D. Adams[15]	44	9	20
P. M. Sanfelippo, et al[16]	23	14	61
R. T. Kirkland, et al[17]	30	12	40
Present Series	17	5	29
TOTAL (excluding Ward)	170	61	36

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Polyhydramnios: The Value of Diagnostic Amniocentesis in Third Trimester Pregnancies

HYON JU KIM, M.D., FRANK TURETZ, M.D., AND ROBERT C. WALLACH, M.D.

Introduction

Amniocentesis for prenatal intrauterine diagnosis during the second trimester has been well accepted by both pregnant women at risk and their obstetricians. The high degree of acceptance is primarily due to the well publicized safety of transabdominal amniocentesis when done with ultrasound monitoring by experienced obstetricians. If diagnostic studies reveal an unacceptable abnormality, the patient has the option to terminate the pregnancy within the usual legal and clinical guidelines for gestational age.

It takes an average of three to four weeks to make a cytogenetic diagnosis from amniotic fluid cell culture. Cytogenetic diagnosis is the main indication for prenatal amniocentesis in more than 90% of the cases in recent study series (1). When alpha-fetoprotein is measured directly in amniotic fluid, it allows for a shorter time to the prenatal diagnosis of open neural tube defects. Often, it takes more than four weeks for specific diagnosis involving errors of metabolism that require specific enzymatic and biochemical tests of cultured amniotic fluid fibroblasts. Because of these technical and legal time limits, amniocentesis for routine prenatal diagnosis is usually performed during early second trimester (14–18 weeks) and is not generally recommended during late second trimester or the third trimester. Intrauterine diagnosis beyond the late second trimester should be considered in selected cases when there is a high degree of suspicion of fetal malformation. Since perinatal mortality is high in pregnancies associated with serious congenital malformations, prenatal identification of a major fetal anomaly might aid the obstetrician and pediatrician in determining appropriate intrapartum and postpartum management. Such studies may also provide the opportunity to prepare the family for the birth of an affected infant with early therapeutic as well as psychological intervention.

Polyhydramnios is one of the conditions with a high incidence of fetal anomalies (2). It becomes apparent only during the latter stage of pregnancy (3). Some of the conditions associated with polyhydramnios, such as diabetes, toxemia, multiple pregnancy and erythroblastosis fetalis are readily diagnosed by conventional tests. With the exception of anencephaly, fetal anomalies responsible for polyhydramnios are not easily diagnosed by conventional tests prior to delivery (4). This paper reports three pregnancies with polyhydramnios in the third trimester without the usual obstetric causes. All three patients, after receiving genetic counseling, agreed to amniocentesis to determine the presence of fetal abnormalities.

Case Reports

Case 1:

A 26-year-old, P.0000, Rh$^+$, white female had polyhydramnios at 35-weeks gestation. Prenatal and family history were noncontributory. Blood pressure and blood sugar were normal. Sonogram at 37-weeks gestation showed a singleton pregnancy and a biparietal diameter (BPD) compatible with 35.5-weeks gestation. Following counseling, amniocentesis was done at 37-weeks gestation. Amniotic fluid alpha-fetoprotein level was increased: 3.2 I.U./ml(normal <1 I.U./ml.). An amniogram was performed by injecting 10 cc of renografin 60 into the amniotic cavity. The contrast medium was seen passing through the fetal G-I tract. Four days later, a 2466 gm male infant was delivered by cesarean section because of fetal distress. Over 9000 cc of meconium-stained amniotic fluid was found at delivery. No gross external malformations were found at birth. The infant

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From the Division of Medical Genetics, Department of Pediatrics, and the Departments of Radiology and Obstetrics and Gynecology, Beth Israel Medical Center, N. Y. and Mount Sinai School of Medicine, The City University of New York, N. Y.

Requests for reprints should be sent to Hyon Ju Kim, M.D., Division of Medical Genetics, 6T-41, Beth Israel Medical Center, 10 Nathan D. Perlman Pl., New York, N. Y. 10003.

was placed in the neonatal intensive care unit and observed for possible gastrointestinal (GI) obstruction. A flat film of the abdomen showed a double-bubble gas pattern suggestive of duodenal obstruction (Fig. 1). The patient was operated on within 24 hours after birth and found to have an annular pancreas, partial malrotation of the cecum, and adhesive bands extending from the gallbladder to the cecum. The adhesions were lysed and a duodenogastrostomy and gastrostomy were performed. The patient is now two-years old and thriving.

Case 2:

A 40-year-old, para, 1011, white female seen for the first time at 29.5 weeks gestation had a uterus found to be about 34-weeks size. Sonogram showed a singleton pregnancy with marked polyhydramnios. The fetus' BPD was 5.3 cm compatible with 23-weeks gestation. Because of polyhydramnios with fetal growth retardation, the patient was advised of the possibility of a fetal anomaly and agreed to have amniocentesis for chromosome study and alpha-fetoprotein determination.

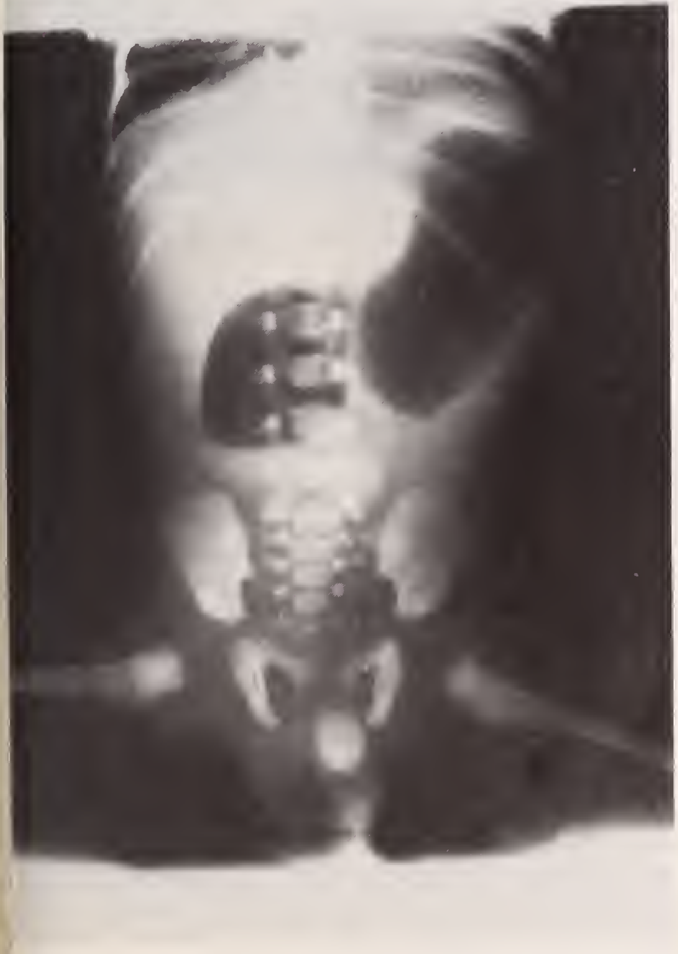

Fig. 1. Case 1. Flat film of abdomen showing double bubble gas attern suggestive of duodenal obstruction.

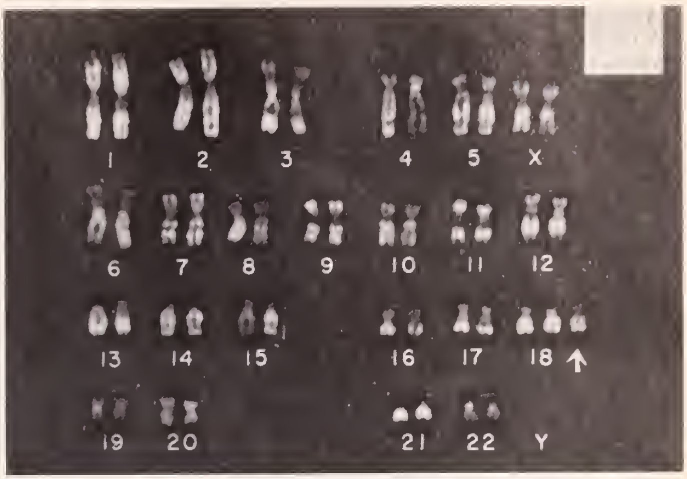

Fig. 2. Case 2. Q banding karyotype of cultured amniotic fluid cells showing Trisomy 18 (47,XX,+18).

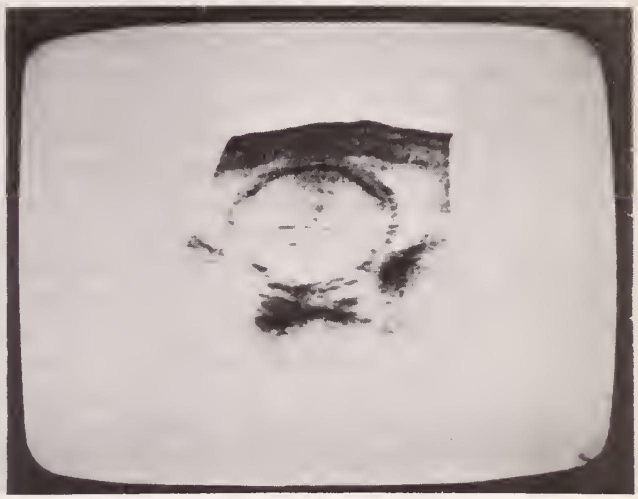

Fig. 3. Case 2. Sonogram showing double contour of fetal head suggestive of fetal demise.

Repeat sonogram at 32-weeks gestation, prior to tap, again suggested intrauterine growth retardation. Chromosome analysis of cultured amniotic fluid cells revealed trisomy 18(47,XX,+18) (Fig. 2). The patient was counseled concerning the prenatal diagnosis of Trisomy 18 Syndrome. An initial reaction of disbelief, was followed by a request for termination of the pregnancy. It was explained that termination at 35 weeks pregnancy carried a maternal risk and that the baby might be delivered alive. A week later the patient had shortness of breath and noted the lack of fetal movement for a few days. She was admitted for therapeutic amniocentesis to relieve shortness of breath and further observation. The fetal heart was not audible. Removal of 1200 cc of clear amniotic fluid with an L/S ratio of 0.8 relieved symptoms. Fetal sonogram (Fig. 3) at 37-weeks gestation showed a

BPD of 6.6–6.7 cm. (28-weeks size). The suggestion of a double contour of fetal head and the absence of fetal heart tones suggested demise. It was elected to induce labor. Cloudy yellow amniotic fluid (1380 cc) was removed and 40 mg of prostaglandin F20C (Prostin, Upjohn) was injected. Seven hours later the patient spontaneously delivered a macerated stillborn female with priminent occiput, low set ears, epicanthal folds, small chin, flexion deformity of fingers, single transverse palmar crease, short sternum and rocker-bottom feet. Autopsy revealed a ventricular septal defect in the heart but no GI obstruction. The umbilical cord had two vessels. Postnatal confirmation of Trisomy 18 was made from cultured cells from amnion.

Case 3:

A 33-year-old P.0000, O^+, serology negative, East Indian female, was referred for prenatal diagnostic amniocentesis at 34-weeks gestation because of polyhydramnios. Sonogram revealed marked polyhydramnios and poor visualization of fetal head with inability to obtain a midline echo (Fig. 4). BPD was compatible with 29.5-weeks gestation. Diagnostic amniocentesis was done for alpha-fetoprotein determination and chromosome analysis and, subsequently, 3000 cc of amniotic fluid was removed and contrast medium introduced. Amniogram revealed no gross fetal anomaly or GI obstruction. Alpha-fetoprotein level (0.4 I.U.) was normal for gestational age. One week later, the patient delivered a 1660 gm premature infant. At birth, multiple congenital anomalies were noted (Fig. 5): microcephaly (Head circumference, 26 cm) with narrow forehead, decreased biparietal diameter, microophthalmia, hypotelorism, a single-nostril nose ending without septum, and cleft palate. The diagnosis of cebocephaly was made and the parents counseled. Since the single-nostril nose ended blindly there was an immediate need for an oral airway. The parents decided that no aggressive measures be taken, and the baby died the next day. Postmortem examination confirmed the diagnosis of cebocephaly. The brain (Fig. 6) showed a single cerebral cortex due to failure of midline cleavage of the forebrain, a single fixed optic nerve, single cranial fossa, and absence of corpus callosum, septum and fornices. The persistent inability to obtain a midline echo on sonogram was explainable by the lack of the midline structures which contribute to the midline echo (5).

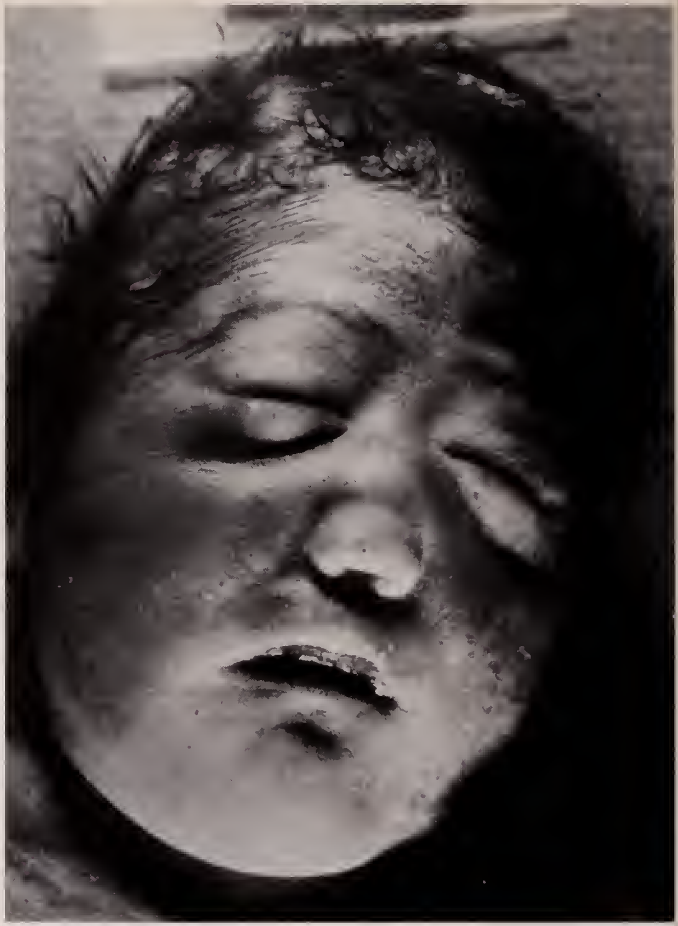
FIG. 5. Case 3. Facial features showing microcephaly, microphthalmia with ocular hypotelorism and single nostril nose (cebocephaly).

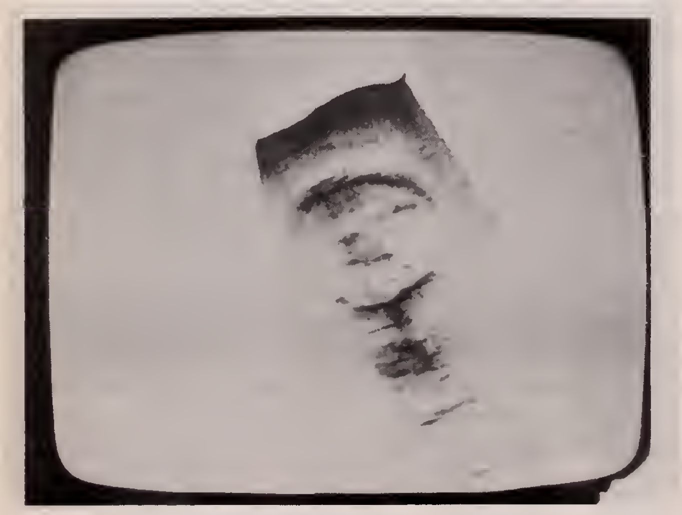
FIG. 4. Case 3. Sonogram showing poor visualization of fetal head with inability to obtain midline echo.

Discussion

Amniotic fluid is a dynamic pool derived from various maternal and fetal sources that can be totally replaced over a three-hour period (6). Thus, an alteration in the total amount of amniotic fluid may result from various pathophysiologic forces. Its underlying mechanism is not always clearly demonstrable.

Polyhydramnios can occur during an otherwise normal pregnancy; however, it has been observed frequently in

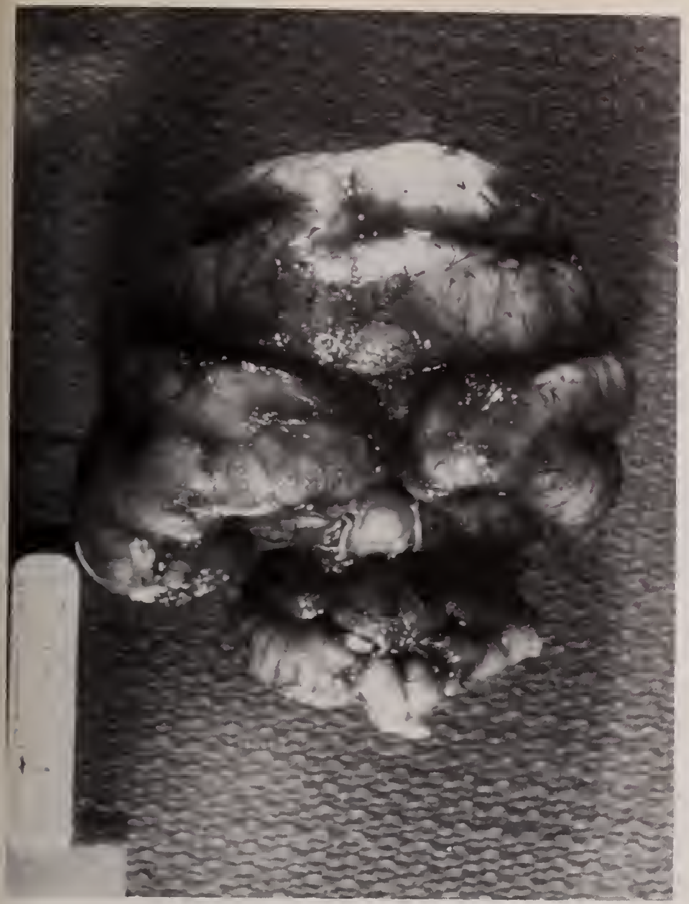

FIG. 6. Case 3. Brain showing single cerebral cortex due to failure of midline cleavage of forebrain.

association with abnormal pregnancies having maternal and/or fetal pathology. In large series with polyhydramnios, it has been shown that after excluding maternal pathology such as diabetes, toxemia, multiple pregnancy and feto-maternal isoimmunization, the remaining one-third to one-half of polyhydramniotic pregnancies have fetal malformations (2,4,7,8). These included hydrops fetalis, anencephaly, hydrocephaly, meningomyelocele, inencephaly, esophageal atresia, duodenal atresia, jejunal atresia, annular pancreas, omphalocele, sacroccygeal teratoma, multiple congenital anomalies including cardiac malformation, and chromosomal aberrations. The most common anomalies involve upper GI tract obstruction and central nervous system (CNS) malformation. Impairment of fetal deglutition, functional with CNS anomalies and mechanical with upper GI obstruction, is believed to be responsible for the genesis of polyhydramnios.

Sonographic study will show gestational age, single or multiple pregnancy, size of placenta and gross fetal anomalies such as anencephaly, hydrocephaly, and any mass in addition to excessive amount of amniotic fluid (9). By amniogram, fetal contour may be visible delineating gross external fetal abnormalities including soft tissue masses (10). The swallowed contrast medium can outline the fetal GI tract, allowing evaluation for obstruction (10,11). However, as in Case 1, the x-ray may not exclude GI obstruction. In spite of passage of the contrast medium through the GI tract on amniogram, upper GI obstruction was suspected in view of increased alpha-fetoprotein, polyhydramnios, normal fetal head on sonography and absence of other soft tissue abnormalities in the amniogram.

In 1972, Brock and Sutcliffe reported elevated alpha-fetoprotein in amniotic fluids from pregnancies associated with anencephaly and meningomyelocele (12). Since then, determination of alpha-fetoprotein in amniotic fluid has been used widely as a prenatal screen for open neural tube defects. It is believed that elevated alpha-fetoprotein in amniotic fluid is caused by transudation through an open neural tube defect. Elevated alpha-fetoprotein in amniotic fluid has also been described with upper GI obstruction (13), omphalocele (14), congenital fetal nephrosis (15), fetal sacrococcygeal teratoma (16) and fetal death. Therefore, alpha-fetoprotein determination is diagnostic in most common fetal anomalies associated with polyhydramnios such as CNS anomalies and upper GI obstruction and is a further indication that fetal pathology is present. Increased level of alpha-fetoprotein in upper GI obstruction is the result of impairment of fetal swallowing of amniotic fluid. The outcome of pregnancy is very good with early surgical correction in isolated upper GI obstruction, and the child can lead a normal life. However, in Down's Syndrome duodenal atresia can occur frequently. Therefore, a chromosome analysis of cultured amniotic fluid cells should be done if fetal upper GI obstruction, especially in pregnancies with advanced maternal age, is suspected.

In Case 2, the mother's advanced age and evidence of fetal growth retardation by sonography led to a suspicion of a fetal chromosome aberration. More than half of all Trisomy 18 Syndrome have been associated with polyhydramnios (17), with upper GI obstruction being less common than in Down's Syndrome. The mechanism for polyhydramnios in the Trisomy 18 Syndrome is unclear. There is a high incidence, however, of a small placenta and single umbilical artery (17) which might contribute to hemodynamic changes and polyhydramnios.

In Case 3, diagnosis of cebocephaly was not made prenatally. Counseling given prior to amniocentesis enabled the couple to accept the infant's abnormality and allowed them time to reach their decision not to have major life-saving medical intervention shortly after birth.

Summary

Complete prenatal diagnosis should be considered even in the third trimester of pregnancy when fetal anomaly

is under suspicion. The information gained by such diagnostic studies may be beneficial to the family and their obstetrician and pediatrician in managing the pregnancy, in the delivery, and in anticipating correctable malformations.

Pregnancies associated with polyhydramnios without obstetric causes, should be studied since the incidence of fetal anomaly is high. Elevation of alpha-fetoprotein in amniotic fluid will be a further indication of fetal anomalies, especially most common fetal anomalies associated with polyhydramnios such as open neural tube defects and upper GI obstruction. Chromosomal analysis of cultured amniotic fluid cells should be done to define the basis of the anomalies. The information is crucial for the management of pregnancy and delivery.

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Medical Report on Casualties in the Hokuriku Tunnel Train Fire in Japan with Special Reference to Smoke-Gas Poisoning

A. KUTSUMI, M.D., Y. KUROIWA, M.D., and R. TAKEDA*

Abstract

We report the clinical and laboratory findings of nearly 400 victims from the train fire accident in the Hokuriku Tunnel that occurred on November 6, 1972. The chief symptoms of these victims were caused by injuries to the respiratory system, by inflammatory processes of the larynx, and by bronchopulmonary disturbances. The evident CO encephalopathy rarely was observed, except in two cases with an interval form of CO poisoning that completely improved in several months.

Based on our conclusion that the main sequelae of the Hokuriku Tunnel Train Fire were attributable to smoke and irritative noxious gases, we recommend that prevention of such fire accidents in the future should include the study of specific constituents of irritative gases or chemicals in the smoke.

A train fire in the second longest tunnel in Japan resulted in more than 400 casualties suffering from smoke and gas inhalation on the night of November 6, 1972. There have been some reports on large scale carbon monoxide poisoning in coal mine accidents in Japan (1-3). However, no report on a train tunnel fire summarizing so many cases has ever been noted. Therefore, we would like to report the outline of the clinical manifestations of the tunnel fire casualties and to discuss the problems in such an underground fire.

Description of the Tunnel Fire

The Hokuriku Tunnel is the second longest tunnel in Japan, 13.8 km long. About nine minutes after the Express Kitaguni, a northbound, 13-car-formation train, departed Tsuruga Station at 1:04 a.m., a fire occurred in the no. 3 (dining) car. The train was in the tunnel and stopped immediately about 5 km from the Tsuruga entrance (Fig. 1). At once, the electrical supply to the tunnel was cut off. Although the fire was limited to the dining car, smoke filled the tunnel. The 760 passengers tried to leave the train, and wait for rescue; many were moving outside the train to the exits of the tunnel, when they were overcome by the smoke.

Rescue and Emergency

About 140 escaped by themselves from the Imajo entrance, and 28 from the Tsuruga entrance (Fig. 1). The remaining passengers were rescued by relief train or motor cars. From the Tsuruga entrance, rescue transports were made four times between 2:37 a.m. and 11:00 a.m., and from the Imajo entrance three times between 4:10 a.m. and 10:00 a.m. Some of the casualties were treated by the field medical group, but the majority was transferred to hospitals, or medical facilities in the cities of Tsuruga, Takefu and Sabae.

The Situation After the Rescue

On the day of the accident, 750 out of 760 passengers were treated, and 422 were admitted to hospitals. The next day, 37 were discharged. On the second hospital day, 64 cases out of 385 admitted were considered to be severe including six cases with fracture; 91 were moderately severe and 230 were diagnosed as mild. In general, most of the cases rescued by the first relief group were mild, and the later rescued groups had more serious conditions.

Symptoms on Rescue

According to enquête from 480 victims, 105 cases had disturbances in the level of consciousness, including minimal impairment while in the tunnel. However, the incidence of the disturbances decreased to one-eighth of

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[*] From the Medical Advisory Committee for the Hokuriku Tunnel Train Fire, Kanazawa JNR, Japan. The medical committee members are listed at the end of this report.

Address reprint requests to Dr. R. Takeda, Kanazawa University, Japan.

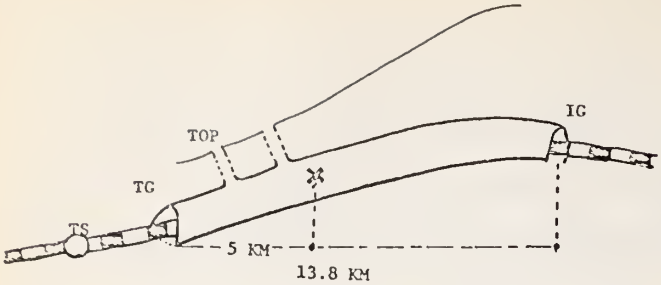

FIG. 1. TS: Tsuruga Station, TG: Tsuruga-guchi (Tsuruga entrance), TOP: Tsuruga oblique pit, X: spot of fire of the train, IG: Imajo-guchi (Imajo entrance).

TABLE I

Rhinolaryngologic Symptoms

(77 cases on 17, 18 hospital days)

Difficulties in phonation (husky voice, hoarseness, etc.)		55 cases (72%)
Difficulty in swallowing (sore throat, etc.)		37 cases (48%)
Disturbance in respiratory system		57 cases (74%)
cough	47 cases	
sputum	36 cases	
black sputum	18 cases	

cases on hospitalization. All showed darkly stained skin with black dust covering the nostrils as well. Mild cases complained of cough, headache, lacrimation, ocular pain, dizziness, and palpitation.

Severe cases had more intensive discoloration of skin, trauma, lacrimation, ocular pain, sore throat, cough, dyspnea, stridor, and chest pain, etc. Two cases showed temperature rises up to 40°C on the second or third days, that were probably caused by bronchopneumonia. Traumatic complications were common with contusions of the head, extremities, and loin in 105 cases, leg sprains in nine cases, and skin lesions in 29 cases. Six patients had bone fractures.

Signs on Admission

Skin and mucous membrane: Skin was darkly stained with smoke. Conjunctive was hyperemic and lacrimation was seen. About 17% of the cases exhibited cyanosis.

Circulatory system: Pulses were usually normal. However, in 97 cases with fever over 38°C, transient tachycardia was noted. One case went into shock. Three patients developed hypertension.

Nose-throat-lung (respiratory system): Most victims had black nasal discharge and laryngeal involvement, such as hoarseness, husky voice, sore throat, and difficulty in swallowing (Table I). Coarse rales were audible in most cases. Dyspnea was marked in three cases, necessitating tracheotomy. Dr. Toyota studied 77 cases on the 17th and 18th hospital days (Table I, II). The nasal cavity showed hyperemia in several cases. The pharynx was almost normal except for a few cases with hyperemia. Vocal cords mostly showed redness and swelling, in some cases atrophic changes, which might be due to the inflammatory processes. There was granulation, or a deposit of a dark particle in the cord.

Neurologic Findings: On the fourth and fifth days, Dr. Kuroiwa studied the inpatients (99 cases) neurologically (Table III). All patients were alert, although five cases had clouding of consciousness on admission, which cleared in a few days. One case showed retrograde amnesia, but no further memory disturbance was seen. No patient showed amnestic syndrome or severe mental changes, which were commonly seen as sequelae of CO encephalopathy in the Miike CO poisoning cases (Table III) (4). In 86% of the cases, there were no neurologic signs, except neck stiffness in five cases, and hyperreflexia in two cases. No rigidity or paralysis was seen. Two cases had traumatic compression fracture of the thoratic spine, which probably occurred by jumping from the train.

Thus, about one week after the accident, there were no neurologic residuals showing the signs of acute carbon monoxide poisoning such as mental or extrapyramidal, although the blood levels of carbon monoxide were not estimated at that time.

TABLE II

Laryngologic Findings on Vocal Cord

(77 cases on 17, 18 hospital days)

Normal		23 cases
Hyperemia		35
slight	27	
moderate	7	
marked	1	
Swelling		11
slight	8	
moderate	3	
Paleness		4
Granulation		6
Deposit of black spots below the mucous membrane		3
Atrophy of the cord		15

TABLE III

Comparison of Hokuriku Tunnel Train Fire and the Miike Coal Mine Accident

	with special reference to neurologic findings on admitted cases	
	HOKURIKU	MIIKE
Time of study	4th hosp. day	17th hosp. day
No. of admitted cases	99	276
Unconsciousness	0	11 (4%)
Severe mental change	0	16 (24%)
Amnestic syndrome	1	119 (43%)
Normal mentation	98 (99%)	80 (29%)

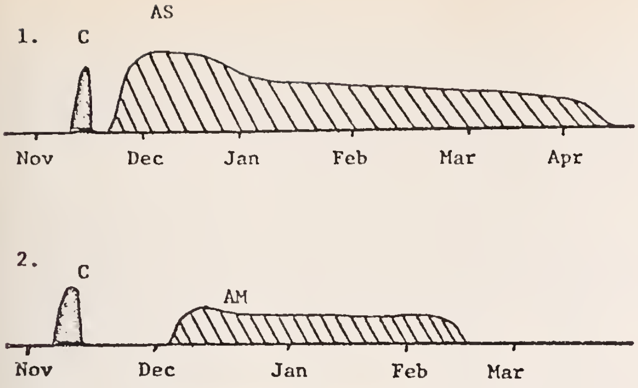

FIG. 2. C: coma, AS: apallic syndrome, AM: amnestic syndrome.

However, three weeks later, two cases developed signs of mental or extrapyramidal involvements compatible to the interval form of acute carbon monoxide poisoning (5).

Case Reports

Case 1: A 65-year-old female (Fig. 2-1) was unconscious when rescued, but was alert in the evening of the second day (about 40 hours after the accident). She was active and had no respiratory difficulty, husky voice, or cough. On November 21 (16th hospital day), she gradually developed disorientation, that was rapidly progressive and on November 25, she became lethargic and mute. She did not take food spontaneously. Neurologic examination showed somnolence, rigidity, mutism and incontinence, but no pyramidal sign was seen. The symptoms progressed, and on December 4, she showed Apallic syndrome (Kretchmer) (no mental reaction, mute, preserved sleep and wake cycle) and generalized rigidity. She could not swallow at all, and was kept on tube feeding. In the middle of December she showed slight response to speech by nodding, and in February 1973, some facial expression reappeared, and she could answer with simple words. In March, she could swallow, and speak, and gait became possible in a go-cart. Around this time she rapidly improved, and by April mental symptoms, such as mutims, apathy, and disorientation had completely disappeared. She retained the memory of the accident. No apraxia, aphasia and rigidity were seen.

Case 2: A 53-year-old man (Fig. 2-2) was rescued nine hours after the accident, when consciousness was normal. He had lost consciousness in the tunnel and could not recall how he was rescued. On admission he had respiratory symptoms with atelectasis in the right lower lung field, but he was normal neurologically. From December 6 (30th hospital day) on, slips of memory became gradually pronounced, and motion became slow. In the middle of December he developed rapidly marked disorientation, disturbance of recent memory, and apraxia (constructive), although, otherwise he remained normal neurologically. The draw-a-man test was very clumsily done and acalculia was seen. Right-left orientation was preserved. Thereafter he gradually improved, and by the middle of February, 1973, these mental symptoms had almost disappeared.

Summary of the Two Cases: These cases became unconscious for a short period probably due to CO poisoning, and improved completely. Then about three weeks later, mental and neurological symptoms reappeared. These are considered to be interval form of CO poisoning (5).

Laboratory Examinations

Urine: Transient glycosuria was observed in the early stage in 7.1% of the cases examined, and proteinuria was positive in 22.1%.

Sputum: There were often black spots in the sputum. The size of the black particles were 20-50 microns in diameter larger than ordinary dust.

Feces: In the early stage, stool specimens contained darkly stained material, probably from the ingestion of smoke dust through the mouth.

Leukocytosis was over 8100/cmm^3 and seen in 40.4% of cases a week after the accident, and, in 11 cases, reached the level of 20,000/cmm^3 or more. It usually normalized rapidly, and within several days only 7% showed leukocytosis. RBC count showed no significant change. ESR acceleration was common in the early stage. Blood chemistry showed a transient rise of serum LDH level, GOT level, NPN or BUN level. Rales, increased ESR and leukocytosis were observed more in victims with disturbance of consciousness, and the incidence of abnormal findings that developed in the acute stage appeared to be related to the age of the victims, except for proteinuria, as depicted in Figures 3 and 4. Most of the abnormalities in the blood chemistry, however, became normal within one to four weeks.

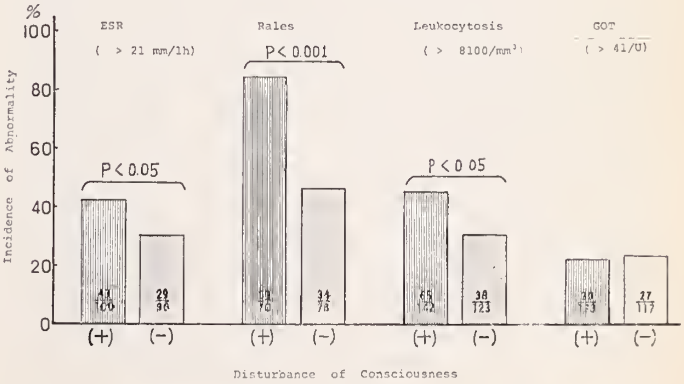

FIG. 3. Relationship between clinical data and consciousness in the acute stage.

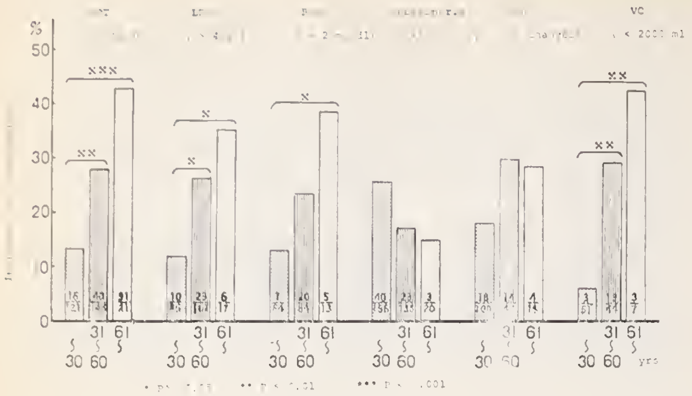

FIG. 4. Relationship between the incidence of abnormal laboratory data and age.

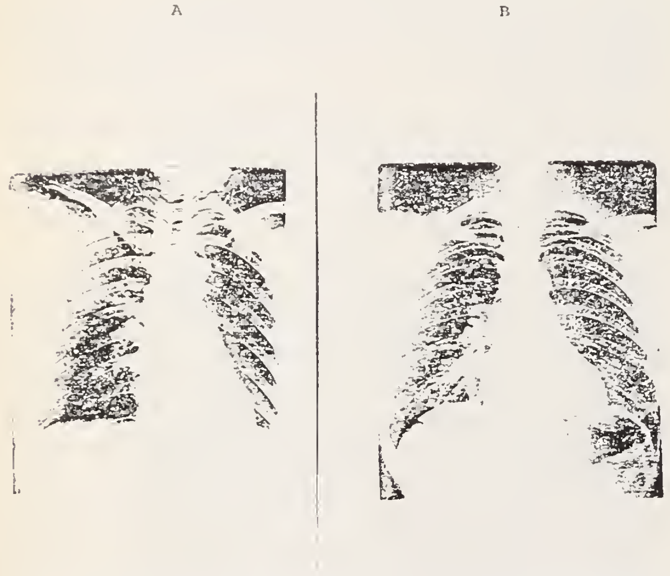

FIG. 5. A: right upper lung field shows pneumonia (a 24-year-old female), B: cardiac enlargement and tram lines (a 52-year-old female).

Chest x-ray: Abnormal findings were observed in about one third of the cases. Abnormal patterns were grouped into tram-line shadow, peribronchial infiltration (including findings of pneumonia) dense linear shadow, reticular shadow over the entire lung fields in addition to shadows of pre-existing diseases. No case showed mottling, spotted or nodular shadows over the entire lung as seen in typical chemical pneumonitis. Subsequent films taken in follow-up studies over the past four years also showed no findings consistent with bronchiolitis fibrosa obliterans as seen after inhalation of special gases such as nitrogen oxides. As for cardiac shadows, an increased C/T ratio (over 55%) was noted in about 20% of cases. It is not possible to relate this to the accident since the films were taken on recumbent position in the severe cases.

Pulmonary functions: A lowered PaO_2 and an elevated $PaCO_2$ were observed in cases with severe respiratory failure. However, blood CO did not reach toxic levels in any of 22 subjects examined within a few days. Decreases in the vital capacity (less than 2000 ml) were noted in 18.6% (19 cases out of 102 patients) studied one week after the accident. Other detailed tests including %FV and gas analysis were incomplete.

Electrocardiogram: Out of 76 studied, three had sinus tachycardia and extrasystole; one had atrial fibrillation and right bundle branch block; three had pulmonary P, 15 had ST-T changes; and one had left ventricular hypertrophy. Many of these ECGs were taken some time after the accident. They could not be directly associated with the accident.

Electroencephalogram: Thirty-four patients were examined within two months (53 recordings). One case showed abnormal change (Interval form of CO poisoning), three cases were slightly abnormal (Interval form of CO poisoning and two others), and 21 were borderline abnormal.

Course

At the time of admission there were 19 serious cases, and they showed relatively rapid improvement. Two weeks later, the only serious cases were 12 out of 199 inpatients. Gradings of severities were studied after one month according to the criteria (Table IV). The number of grade I and II were 44 in total, which markedly decreased into seven within two and a half months after the accident (Table V). The most serious case (grade I) at two and a half months after the accident was a case with CO interval form encephalopathy mentioned previously. Most of the long standing symptoms and signs in the mild cases were cough, hoarseness and sputum.

TABLE IV

Gradings of Severity

Grade I:	Severe physical disturbances; need help for daily life or bedridden
Grade II:	Moderate physical disturbances; possible home life, but outdoor life difficult
Grade III:	Mild physical disturbances; possible light work
Grade IV:	Slight physical disturbances; not difficult in work
Grade V:	No objective sign

TABLE V

Changes of the Grading of Severity in the Hospitalized Cases

Grade	29th hospital day	2.5 month later
I	6	1
II	38	6
III	17	13
IV	80	5
V	17	5
Unknown	–	5
Total no. of cases	158	37

TABLE VI

Duration of Hospital Stay of the Victims

Date after the "Hokuriku-Tunnel-Train-Fire"		2 Weeks	1 Month	3 Months	6 Months	1 Year
Inpatients :	422 (56%)	→ 199	→ 72	→ 23	→ 9	→ 2

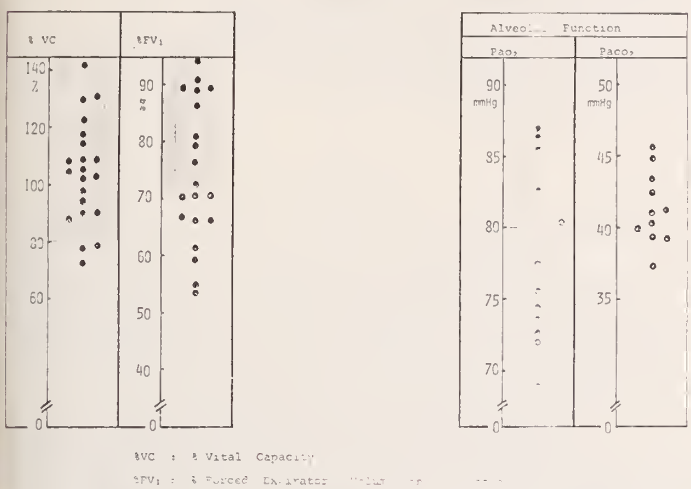

FIG. 6. Pulmonary function in selected patients with chronic respiratory complaints three to four months after the accident.

Duration of hospital stays are listed in Table VI. Follow-up study of pulmonary function was done in a limited number of victims. As depicted in Figure 6, decreased $\%FV_1$ and PaO_2 with increased $PaCO_2$ were noted in patients with chronic respiratory complaints who visited the Kanazawa University Clinic in response to the Committee's request. However, no significant changes were observed in the serial x-ray films of the chest. In some cases, the abnormal findings in gas analysis seemed to be caused by a decreased pulmonary function with aging and in some cases due to a delayed recovery from bronchitis.

Subsequent follow-up examinations, especially of the respiratory system have been done three times during the past four years in patients who responded to the Committee's request. The results will be published elsewhere.

Deaths

There was a total of 30 deaths. Twenty-nine were found dead at rescue, 28 outside and one inside of the train. There were no deaths in the hospital. Measurement of CO in the blood in five deceased victims was performed on the first day, and a 40% saturation of hemoglobin was found.

One week after the accident, a 24-year-old male victim was found in a groove near the tunnel. His blood CO content was 48%. Because of marked decomposition of the body, detailed information was not available. However, there seemed to be no evidence supporting trauma or previous diseases. The respiratory tracts from nasal cavity to segmental bronchus were plugged with black carbon particles. Mucosal change produced by burning which usually is observed in victims burnt to death, was not found in the respiratory tracts, suggesting that the victim inhaled much smoke without heat. Many carbon particles were also discovered in his gastric contents. The death cause in this case was considered to be drowning in a comatose state due to smoke inhalation.

Treatment

Treatment for disturbances in the respiratory system was considered to be most important. Generally the treatment consisted of: (a) oxygen inhalation, (b) antibiotics for prevention of infection, (c) adrenocortical steroids, (d) intravenous fluid supply, (e) medication and pack application for expectoration, (f) inhalation therapy, (h) life saving tracheotomy, and (i) cardiovascular medication or detoxication agents, etc. Tracheotomy was performed in three cases, and two were treated in a hyperbaric oxygenation chamber.

Discussion

The Hokuriku tunnel is one of the longest tunnels in the world. There are scarcely any medical records of injuries due to fire in such a place. In cases of fire in the tunnel or pit, CO poisoning has been thought to be the most important injury.

In the present accident, most of the casualties were from inflammatory processes of the respiratory tract with changes in vocal cords, bronchiolitis, pneumonitis, atelectasis, etc. Only a small number of persons showed signs of CO encephalopathy in contrast to the gas explosion at the Miike Pit.

There have been few detailed reports on the smoke poisoning syndrome. Patients suffering from fire accident frequently show pulmonary complications that may be the primary cause of death (9, 10). The effects of chemical irritants in smoke produced by combustion and, in addition, the direct effect of hot air are suggested for the pathogenesis of pulmonary complications. Pneumonia caused by special gases and bronchiolitis fibrosa obliterans due to gases, including NO_2 (Silo-Filler's disease) and phosgene, have been reported. Since there have been changes in the make up of combustible materials, the possibility of other noxious gas poisonings caused by new construction material are considered. It was recently shown through experimentation that in smoke poisoning the aldehyde generated on burning of wood, cotton, and furniture, is responsible for pulmonary edema (11). In the burned dining car, polyester synthetic resin, vinyl chloride, and vivylidene chloride (Saran) were used for interior decoration. Gases produced by combustion of these new construction materials are know to be CO, HCI, organic chloride gases (phosgene, chlorethane, and acrolein). These organic chloride gases are known to provoke pulmonary edema. In the present accident, the role of chemical irritants in the development of respiratory changes should be most likely. Important therapeutic measures for the victims are those directed at airway obliteration, pulmonary edema and bronchopneumonia.

The development of subacute encephalopathy showing disorientation, amnesia, mutism and extrapyramidal signs, is well considered to be an "interval form of acute carbon monoxide poisoning" (5) due to the typical clinical picture and the time of development (three weeks after the exposure to carbon monoxide). This interval form has been reported clinically as well as pathologically (6,7). This form is given to such cases of carbon monoxide poisoning, in which the acute coma once completely improved, shows recurrence of signs of diffuse encephalopathy after several weeks of normal interval. The pathogenesis of such interval form is not know. However, the existence of such a form should be considered in cases of exposure to acute carbon monoxide poisoning. This concentration and period of inhalation of carbon monoxide might be factors to cause such relapsing form (8).

In anticipation of future fires in underground markets and buildings, preventive methods directed to the specific constituents of the irritative gases or chemicals in the smoke should be studied first.

Medical Advisory Committee of the Hokuriku Tunnel Train Fire

Kuroiwa Y, M.D. Professor of Neurology, Kyushu University, Fukuoka
Sobue I, M.D. Professor of Medicine, Nagoya University, Nagoya
Toyoda B, M.D. Professor of Otorhinolaryngology; President of the Kanazawa University, Kanazawa
Takeuchi J, M.D. Professor of Medicine, Professor of Kanazawa University and present Prof. of Tokyo Medical and Dental University, Tokyo
Takeda R, M.D. Professor of Medicine, Kanazawa University, Kanazawa
Kurakane K, M.D. Professor, Cancer Research Institute, Kanazawa University, Kanazawa
Kutsumi A, M.D. Chairman of the Medical Advisory Committee of the Hokuriku Tunnel Train Fire
Shinagawa A, M.D. President of Sabae City Medical Assoc., Sabae
Seki H, M.D. President of the Takefu City Medical Assoc., Takefu
Nakamura M, M.D. President of the Tsuruga City Medical Assoc., Tsuruga
Hayashi K, M.D. Director, Hayashi Hospital
Kawakami M, M.D. Director, Kawakami Clinic
Takahashi Y, M.D. Director, National Sabae Hospital, Sabae
Shugimoto T., M.D. Professor of Medicine, Toyama Medical and Pharmaceutical University, Toyama

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Cerebrospinal Fluid Ascites Following Ventriculoperitoneal Shunt. Report of a Case and Review of the Literature

JAE M. NOH, M.D., MADHAVA G. REDDY, M.D., AND ROBERT A. BRODNER, M.D.

Introduction

Various types of shunting procedures have been devised for cerebrospinal fluid diversion in patients with hydrocephalus. The ventriculoperitoneal shunt, utilizing a slit-valve silastic catheter, has become increasingly popular since first introduced by Ames in 1958 (1).

A variety of complications have followed the use of the ventriculoperitoneal shunt (2, 3). Ten cases of intraabdominal cerebrospinal fluid collection have previously appeared in the literature. Our report deals with one additional case of cerebrospinal fluid ascites associated with a ventriculoperitoneal shunt performed for hydrocephalus. Diagnosis and therapy of this condition are discussed. Awareness of this complication and the simplicity of its treatment may avoid extensive or unnecessary investigations and procedures.

Case Report

A baby girl was born by normal delivery on June 23, 1976 after a 42-week gestation. Her body weight was 3550 gm, body length was 56 cm and head circumference was 37.5 cm. The pre- and postnatal periods were uncomplicated.

At the age of three months, the child was admitted to the hospital with irritability and vomiting of four-days duration. Her head was abnormally large with a circumference of 47.5 cm. The anterior fontanel was bulging and tense. Setting-sun eyes were present. The remainder of the neurologic examination was normal.

Skull x-rays showed widely separated sutures. Cerebral angiography and air-pantopaque ventriculography demonstrated a midline avascular cyst in the posterior fossa with marked enlargement of ventricles. The cyst was communicating with the ventricular system.

A ventriculoperitoneal shunt was performed. The postoperative course was uneventful and the baby was discharged ten days after surgery.

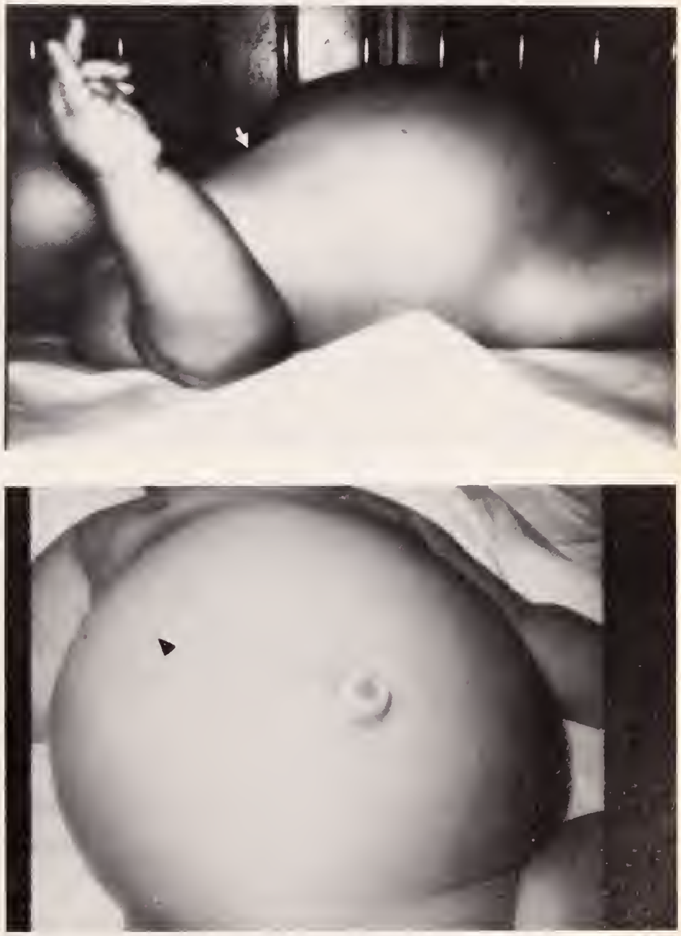

Fig. 1a, b: Pictures showing 5-month-old baby with massive abdominal distension from CSF ascites. a) Notice peritoneal catheter (arrow) and b) abdominal scar (arrow head) for V-P shunt surgery.

From the departments of Neurosurgery and Pediatrics, Mount Sinai Services, City Hospital Center at Elmhurst, New York, N.Y.

Requests for reprints should be sent to Jae M. Noh, M.D. Department of Neurosurgery, City Hospital Center at Elmhurst, 79-01 Broadway, Rm C4-3, Elmhurst, N.Y. 11373.

Two months later, the patient reentered the hospital with diarrhea and abdominal distension. The temperature was 99°F. There was no acute distress. The abdomen was markedly distended but soft and nontender. (Fig. 1). Shifting dullness was present. There was no palpable mass. The head circumference was 47.5 cm. The shunt system was noted to be functioning well by testing the flush valve. The anterior fontanel was flat. Neurologic examination was otherwise unremarkable.

Serial liver function tests, upper gastrointestinal series and intravenous pyelogram were all normal. Abdominal paracentesis demonstrated clear ascitic fluid. Analysis of the fluid revealed a protein content of 1.6 gm%, glucose 90 mg%, WBC 90/mm^3 and RBC 6/mm^3. Gram stain and peritoneal fluid culture showed no organism or growth. No malignant cells were seen.

Despite repeated paracentesis, the abdomen became progressively distended. Revision of the ventriculoperitoneal shunt to a ventriculoatrial shunt was performed. The abdominal distension progressively decreased and completely disappeared within two weeks after surgery. Fourteen months after shunt revision, the baby was normal except for residual head enlargement.

Discussion

Cerebrospinal fluid ascites is an unusual complication of ventriculoperitoneal shunting. It may occur from one day to several years after surgery. In the reported cases (Table I), clinical findings were inconsistent and could not be correlated to suggest an etiology for abdominal fluid collection. The pathophysiology of intraperitoneal cerebrospinal fluid accumulation following a ventriculoperitoneal shunt is unclear. Laboratory and histologic studies of the kidneys, liver, omentum and peritoneum have failed to demonstrate the pathophysiology of the ascites.

Development of ascites may be related to a decrease in the absorptive function of the peritoneum, or overproduction of cerebrospinal fluid beyond the normal absorptive ability of the peritoneum (4, 5). Ray & Peck (4) observed that excessive drainage of cerebrospinal fluid from a choroid plexus papilloma exceeded the rate of peritoneal absorption and caused ascites.

Peritoneal malabsorption is not an uncommon complication in infants under the age of two months (2). It may be related to functional immaturity of the membrane during the first few months of life. However, no peritoneal malabsorption problems were reported in Ames' series of ventriculoperitoneal shunts performed on 42 infants, the majority of whom were under three months old (1). In another large series of 185 infants who had undergone ventriculoperitoneal shunting, 45 (24%) developed various intraabdominal complications but none had cerebrospinal fluid ascites (3). In all but one of the previous cases of this complication, the patients were older than

TABLE I

Reported Cases of Cerebrospinal Fluid Ascites Complicating Ventriculoperitoneal Shunting

Author	Age	Sex	Original Disease	Time interval shunt-ascites	Character of ascitic fluid	Other surgery or associated illness	Treatment	Results
Ray & Peck (4)	4 mos	F	papilloma of choroid plexus	1 day	clear colorless fluid.cl: 108%	Multiple abdominal surgeries	Excision of choroid plexus papillomas	expired
Ames (1)	3 mos		—	2 yrs	—	acute febrile illness	V-A shunt	good
Odeku et al (8)	6 mos	F	communicating hydrocephalus	9 mos	clear straw color protein: 1.3–1.7 gm% cells: numerous culture: (−)	abdominal wound infection V-P shunt revision; nonspecific peritonitis	laparotomy	ascites persist, loss of follow-up
Dean et al (10)	8 mos	M	aqueductal obstruction	About 6 mos	clear straw color protein: 0.9 gm% WBC: 9	laparotomy for omphalocele with wound infection; revision of peritoneal end; DPT injection with febrile episode.	V-A shunt	good
Little et al (14)	—		(details not reported)		—	—	revision of shunt	—
Little et al (14)	—		(details not reported)		—	—	revision of shunt	—
Rosenthal et al (13)	15 mos	F	obstructive hydrocephalus 2 deg. to astrocytoma	10 mos	clear straw color S.G. 1.016 protein: 0.1 gm% cells: 0	biopsy of omentum & peritoneum; (−)	V-A shunt	good
Weidman (6)	10 days	F	aqueductal stenosis	2½ mos	xanthochronic protein: 0.7 gm% cells: 60	biopsy of liver, kidney & other organs: (−)	V-A shunt	good
Parry et al (11)	7 mos	M	communicating hydrocephalus	1 wk	clear culture: (−)	(−)	revision of peritoneal end. revision to V-A shunt	no change good
Cummings et al (9)	53 yrs	M	aqueductal stenosis	18 mos	xanthochronic protein: 1.1 gm% cells: (−) culture: (−)	multiple shunt revisions	V-A shunt	good

three months (6). Therefore, younger age and peritoneal immaturity in itself is unlikely to be the cause of cerebrospinal fluid malabsorption.

Peritoneal infection might block the draining lymphatics by white blood cells and cellular debris. The resultant build-up of protein in the peritoneal cavity and associated increase in colloid osmotic pressure could cause failure of fluid absorption. Inability of the peritoneum to absorb fluid even in cases of mild peritonitis has been observed (7). Odeku et al (8) and Weidman (6) described cerebrospinal fluid ascites complicating ventriculoperitoneal shunts in patients with peritonitis, proven histologically but not manifested clinically. Abdominal paracentesis in our own case demonstrated high protein content with many white blood cells. This may have been a manifestation of subclinical peritonitis.

Several patients who developed cerebrospinal fluid ascites after ventriculoperitoneal shunting had a past history of laparatomy or shunt revision (4, 8–10). Similarly, local cystic accumulation of intraabdominal cerebrospinal fluid following ventriculoperitoneal shunting has also followed previous abdominal surgery or shunt revision (11,12). The relatively small peritoneal opening for shunt placement may be a significant factor in the pathogenesis of peritoneal malabsorption as suggested by Parry et al (11). However, previous peritoneal manipulation may contribute to a decrease in its absorptive function.

Dean and Keller (10) speculated that malabsorption of peritoneal fluid in their case may have been related to an immune reaction secondary to a routine DPT injection.

Summary

Intractible ascites following ventriculoperitoneal shunting for hydrocephalus is a rare complication, with only ten cases reported in the literature. The accumulation of cerebrospinal fluid in the abdomen is probably not secondary to pathology in the liver, kidney, or other intraabdominal organs, but may be related to a defect in peritoneal absorption or a relative inability of the normal peritoneum to handle an excessive fluid load. Manipulation of the peritoneum prior to shunt surgery and clinical or subclinical peritonitis may also be factors. Extensive or aggressive investigation for ascites should be avoided unless clinically indicated. Multiple paracentesis is ineffective; the most appropriate management is to remove the peritoneal catheter and transfer it to another site.

Regardless of possible pathophysiology, diversion of cerebrospinal fluid to an area other than the peritoneal cavity has been uniformly followed by a gradual decrease in ascitic fluid.

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Femorotibial Bypass for Limb Salvage*

M. HAIMOV, M.D.

Introduction

The feasibility of extending vascular reconstructive procedures to the branches of the popliteal artery has been documented with increasing frequency. (1–19) Twelve patients who underwent femorotibial bypass in the last four years form the basis of this report. The purpose of this presentation is to confirm the clinical applicability of this approach to limb salvage situations with special emphasis on the extent of gangrene that is still compatible with foot salvage.

Materials and Methods

Femorotibial bypass was done in 12 patients during th last four years (Table I). They ranged in age between 4 and 82 years old. All patients had severe rest pain an would have required a major amputation unless a successful revascularization procedure could be carried ou eight of the patients were diabetic and nine had variou degrees of gangrene involving one or more toes an portions of the foot. Major foot infection with planta abscess was present in four of these patients.

TABLE I

Case	Pathology	Age	Rest pain	Diabetes	Patent 1 year	Patent 2 years	Major amputation	Operation-bypass
1	Gangrene rt 1st toe and lateral portion of foot	51	yes	yes	yes	yes	no	Femor-ant. tibial artery (AVG)*
2	Gangrene lt 1st and 2nd toe and lateral portion of foot	46	yes	yes	yes	yes	no	Femoro-post. tibial artery (AVG)
3	Gangrene rt 1st and 2nd toes, gangrenous ulcer of rt heel, necrosis of Achilles tendon	62	yes	no	yes	no**	no	Femoro-post. tibial artery (AVG)
4	Thrombosed popliteal artery aneurysm	52	yes	no	yes	no***	no	Femoro-post. tibial artery (AVG)
5	Gangrene of lt 2nd and 3rd toes	70	yes	no	no	no	yes	Femor-ant. tibial artery (Impragraft)
6	Gangrene of 5th toe, rt	72	yes	yes	no	no	yes	Femoro-ant. tibial (Impragraft)
7	Popliteal artery trauma (high velocity bullet)	46	yes	no	yes	yes	no	Femoro-post. tibial bypass (AVG)
8	Failed femoropopliteal bypass	42	yes	yes	yes	yes	no	Femoro-ant. tibial bypass (AVG)
9	Gangrenous ulcers, lateral portions of rt foot and tips of 3rd and 4th toes, plantar abscess	82	yes	no	yes	yes	no	Femoro-post. tibial bypass (AVG) post-tibial endarterectomy
10	Gangrene 2nd, 3rd and 4th toes, plantar abscess	46	yes	yes	yes	yes	no	Femoro-ant. tibial bypass (AVG)
11	Gangrene 1st and 2nd toes	69	yes	yes	yes	—	no	Femoro-ant. tibial bypass (AVG)
12	Gangrene 4th and 5th toes	67	yes	yes	yes	no	no	Femoro-ant. tibial bypass (AVG)

* AVG—Autogenous vein graft.
** Died at 18 months from acute myocardial infarction.
*** Died from subarachnoid hemorrhage.

Femoral angiography demonstrated an occluded pop

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From the Department of Surgery, Mount Sinai School of Medicine of The City University of New York, N.Y.

Requests for reprints should be sent to M. Haimov, M.D., The Mount Sinai Hospital, Department of Surgery, One Gustave L. Levy Pl., New York, N.Y. 10029.

liteal artery with partial or complete occlusion of the superficial femoral artery in all patients. An autogenous saphenous vein was used in eight patients and PTFE grafts were used in two.

Results

The bypass remained open in eight patients in the immediate postoperative period and limb salvage was achieved in all cases. In seven patients, transmetatarsal amputation of one or more toes was required including portions of the foot. Plantar abscesses were drained in two cases and subsequent split thickness grafts were performed in two patients. A functional and pain-free foot was achieved in all ten patients and all amputation sites healed successfully. In the two patients in whom the bypass occluded in the immediate postoperative period, a below-knee amputation was required. Two patients have died in the follow-up period, one from acute myocardial infarction and one from subarachnoid hemorrhage. In two patients, the bypass occluded during the first year after surgery. None developed symptoms or signs requiring further treatment.

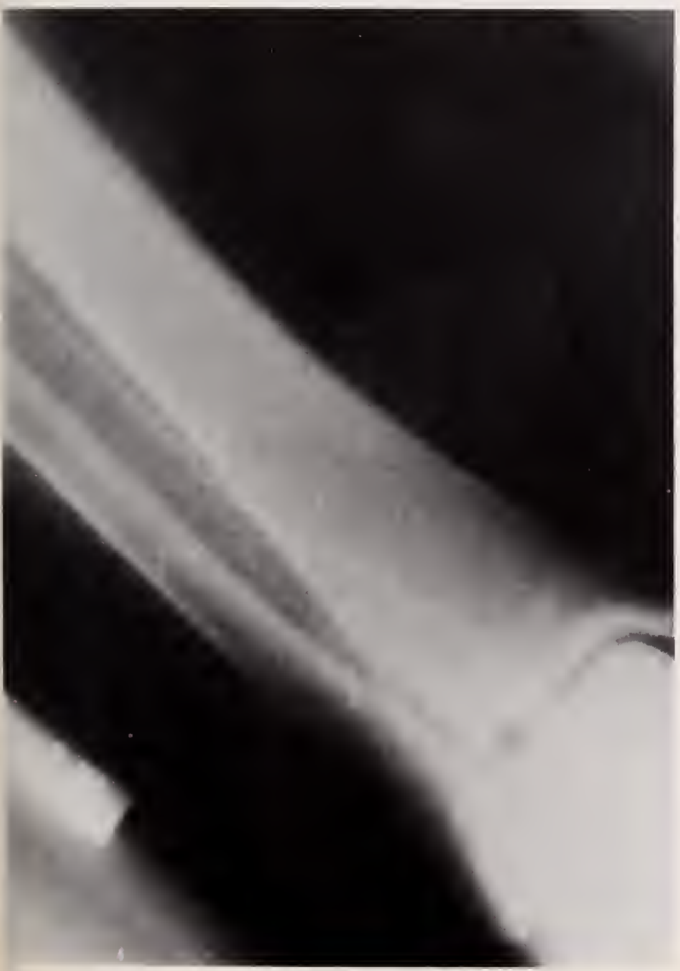

FIG. 1. Case 1. Patent distal anterior tibial artery.

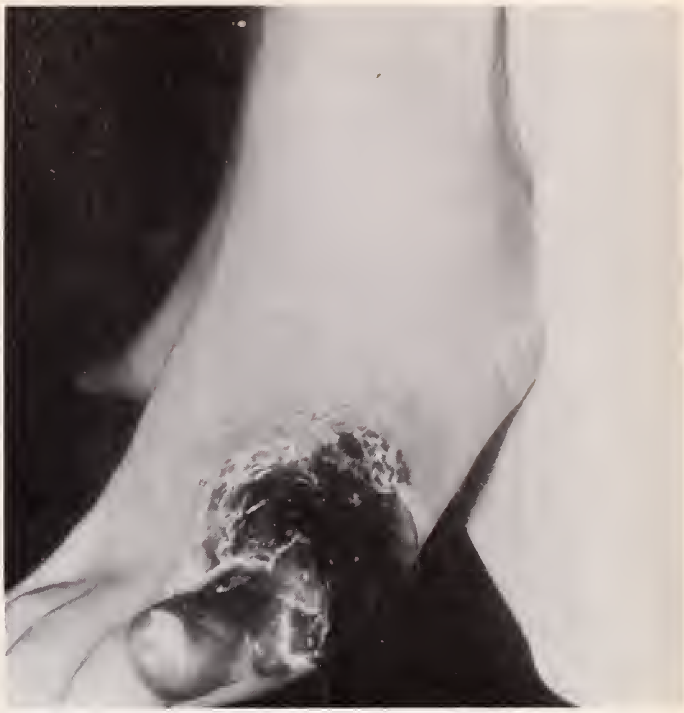

FIG. 2. Case 2. Gangrene of fifth toe and lateral portion of foot.

Case Reports

Case 1:

A 51-year-old male was admitted to the hospital because of pain in the right lower extremity with gangrene of the fifth toe extending along the lateral portion of the foot. Three months earlier, an arteriogram had shown distal superficial femoral artery occlusion and complete popliteal artery occlusion. A lumbar sympathectomy was performed with no significant effect. On physical examination, both femoral pulses were palpable; however, there were no distal pulses palpable in either leg. The right foot showed changes consistent with severe ischemia including skin atrophy, pallor on elevation and dependency rubor. A repeat arteriogram revealed the same findings as previously described, with only the anterior tibial artery being patent in the distal portion of the leg (Fig. 1). The patient underwent a femoroanterior tibial bypass with an autogenous saphenous vein extending from the common femoral artery to the anterior tibial artery right above the ankle. The fifth toe and head of the metatarsal were amputated and the area was left open for secondary healing. The wound healed completely in six weeks, and the patient returned to his previous occupation.

Case 2:

A 46-year-old diabetic was admitted because of resting pain and gangrene of the left foot involving the entire fifth toe and lateral portion of the foot (Fig. 2). Femoral

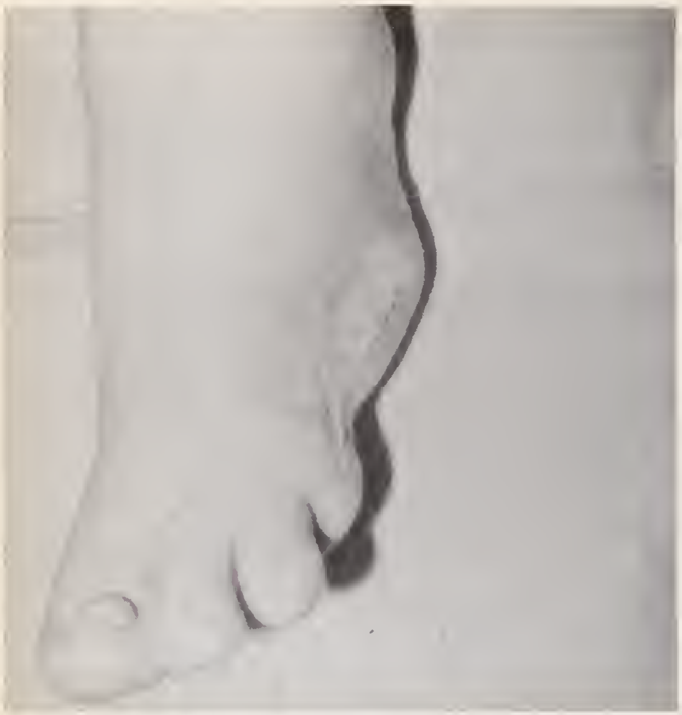

FIG. 3. Case 2. Healing following bypass, partial foot amputation and skin grafting.

arteriography showed complete occlusion of the superficial femoral and popliteal arteries, with both anterior and posterior tibial arteries patent at the ankle level. A left lumbar sympathectomy and a femoroposterior tibial bypass were performed using autogenous saphenous vein. Following surgery, the patient developed excellent posterior and anterior tibial pulses. Five days following the bypass, a transmetatarsal amputation of the fifth and fourth toes was performed including gangrenous portions of the foot. The wound was allowed to granulate and was covered two weeks later with a split thickness mesh graft. Excellent healing was achieved and the patient was able to return to his previous occupation as a baker (Fig. 3).

Case 3:

A 62-year-old white male was admitted to the hospital because of pain in the right foot and gangrene of the right first and second toes, the right heel, and the posterior portion of the right distal third of the leg. Three months prior to this admission, the patient had had surgery for a ruptured aortic aneurysm. He had a complicated postoperative course and developed popliteal artery occlusion. Gangrene developed following unsuccessful embolectomy. The right first and second toes, (Fig. 4), the medial portion of the heel, (Fig. 5), and the posterior portion of the distal third of the leg with complete necrosis of the Achilles tendon, (Fig. 6) were involved. Femoral arteriogram showed complete occlusion of the popliteal artery with a patent posterior tibial artery at the level of the ankle, (Fig. 7). A superficial femoral artery to posterior tibial artery bypass was performed using a reverse autogenous saphenous vein. The posterior tibial and dorsalis pedis pulses were excellent following surgery. The first and second toes were amputated, the ankle was debrided, and the Achilles tendon was tran-

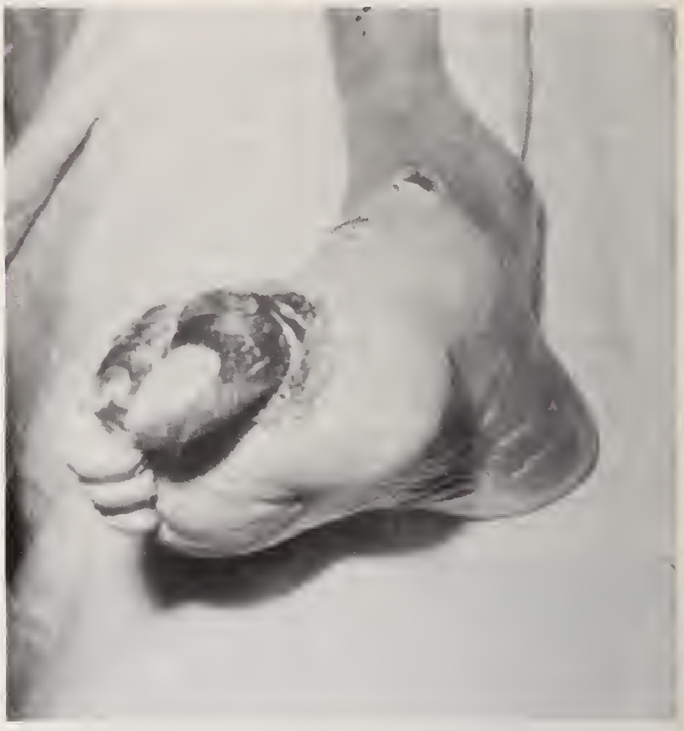

FIG. 4. Case 3. Gangrene of first and second toes.

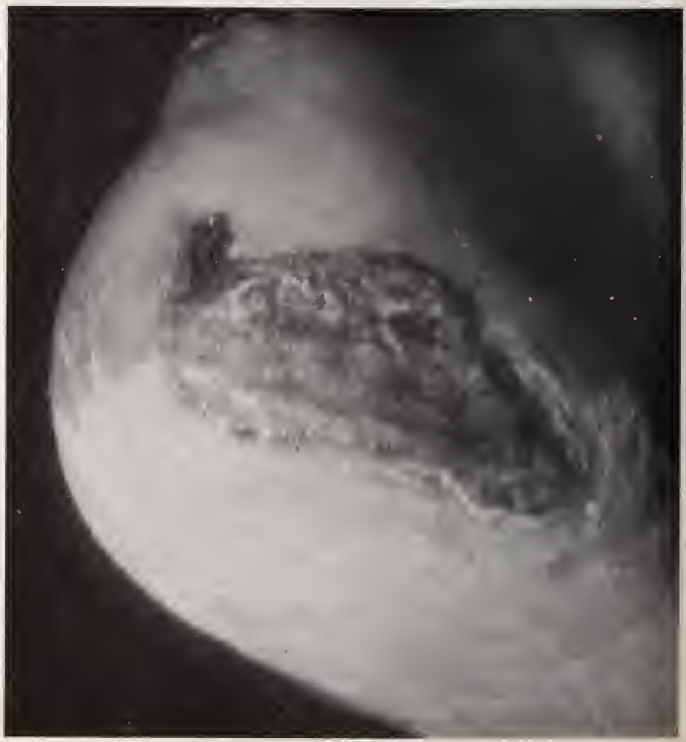

FIG. 5. Case 3. Gangrene of the heel.

sected completely. The amputation site healed per primum and the ankle and Achilles tendon bed healed secondarily (Fig. 8, 9). The patient was able to return to a full-time occupation that involved heavy physical work. He died eighteen months following surgery from acute myocardial infarction. Three months prior to his death

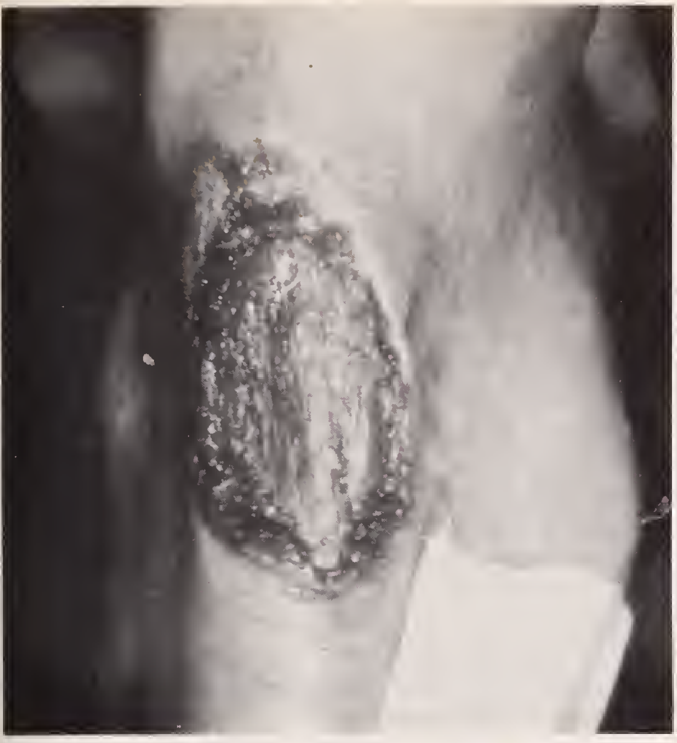

FIG. 6. Case 3. Gangrene of Achilles tendon.

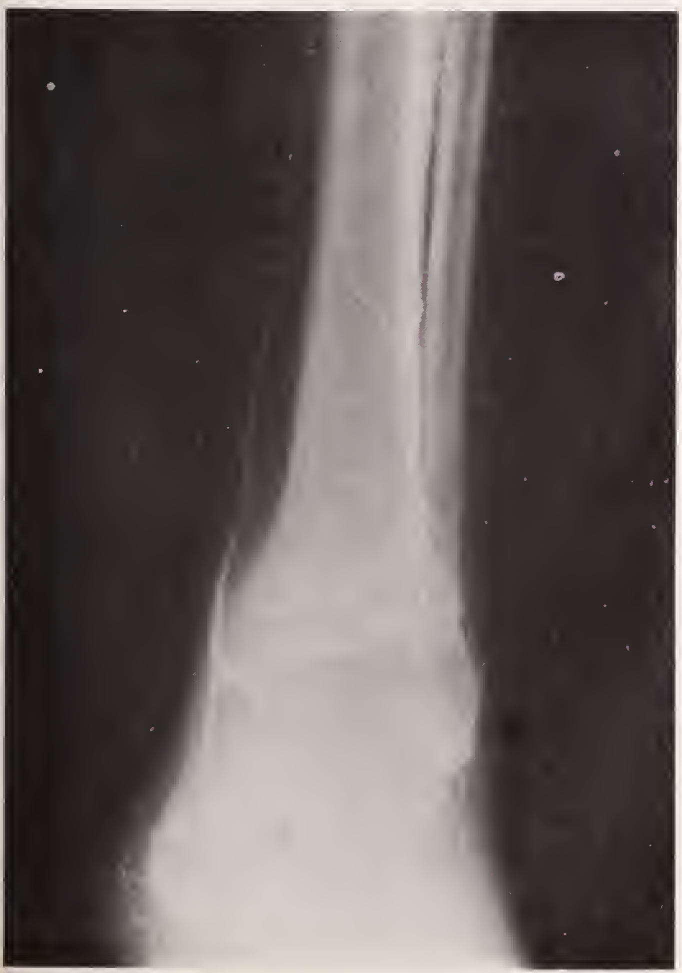

FIG. 7. Case 3. Patent posterior tibial artery.

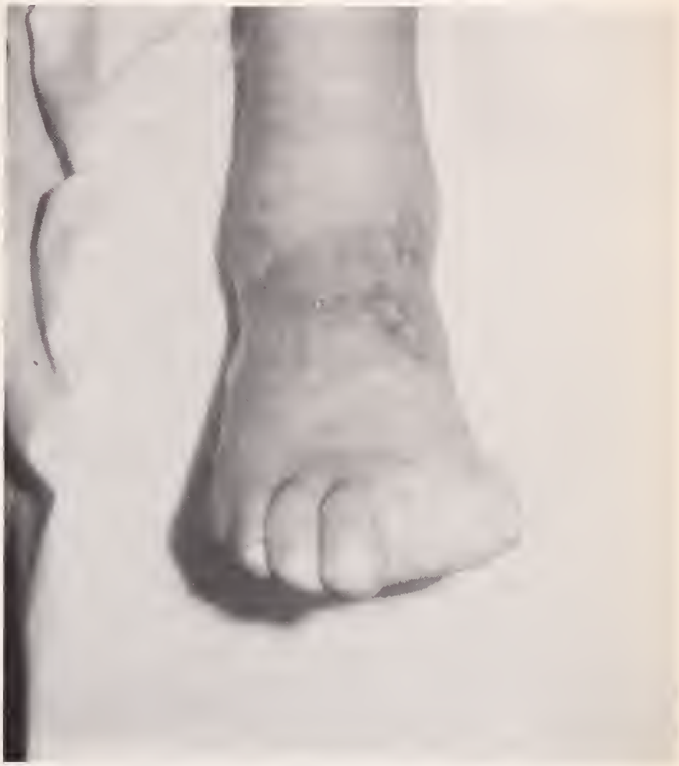

FIG. 8. Case 3. Healing following bypass and toes amputation.

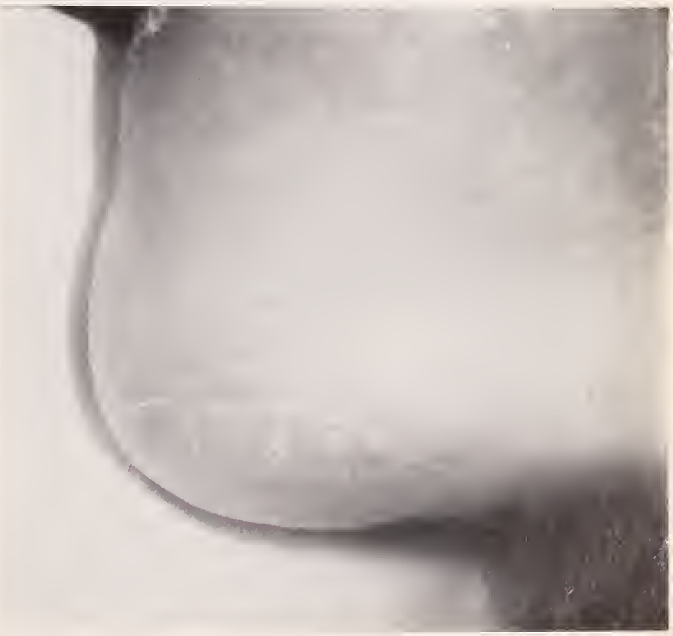

FIG. 9. Case 3. Healing of gangrenous heel ulcer following successful femorotibial bypass.

the bypass occluded and the patient developed coolness of the foot with mild discomfort after prolonged standing. This situation was clinically manageable and no further treatment was required. Ironically, he developed his myocardial infarction while attempting mountain climbing.

Discussion

The feasibility of carrying vascular reconstructive procedures to the distal portions of the leg has been demonstrated previously. The experience in this report confirms the value of these procedures in limb salvage situations. The overall results are comparable to previous reports of similar or much larger groups of patients (1, 3–19). It is hoped that the more detailed case documentation in this report will prove of value to surgeons not closely acquainted with the degree of tissue loss coupled with adverse angiographic findings that is still compatible with limb salvage. The indication for femorotibial bypass is gangrene or severe foot ischemia that will require below-knee or above-knee amputation for treatment. This author and most of the reports in the literature agree with this statement. Diabetes and the presence of localized infection do not seem to be contraindications. The extent of foot gangrene should be such, that following limited amputation and healing, the preserved foot would be both painless and functional. A careful angiographic evaluation is of utmost importance to determine the feasibility of femorotibial grafting. The use of tournique-induced reactive hyperemia, exposure of delayed films up to forty seconds after injections at the time of angiography, and intraoperative angiography are all helpful maneuvers in arriving at an overall correct surgical decision. (2, 7, 8). Demonstration of the presence of a patent plantar arch has been stressed as being a prerequisite for successful outcome (7, 8). The autogenous saphenous vein seems to be the ideal type of arterial substitute for this type of surgery. Failure of a distal bypass does not seem to convert a below-knee amputation to an above-knee. Late failure of the graft after healing of partial foot or toe amputation has been achieved, is not necessarily followed by the reappearance of gangrene (8). The surgical risk of this operation is not greater than that of an amputation, and the mortality in all series has been low.

At the time of surgery injection of heparinized saline into the distal vessel to be used for anastomosis will give the surgeon an idea of the degree of peripheral resistance. High peripheral resistance is incompatible with a successful outcome. All patients were taken to the operating room with a consent for a below-knee amputation, since if the operative findings indicate that successful bypass would be highly unlikely, amputation is carried out without delay. Five patients in whom the femorotibial bypass was contemplated but not carried out are not included in this report.

Construction of a small vessel anastomosis with a catheter stent will prevent inadvertant stenosis at the anastomotic outflow. The use of 6-0 or 7-0 vascular sutures and magnification technique are helpful in attaining meticulous technique. Grafts to the posterior tibial artery, which is the artery of choice for bypass, can be brought subcutaneously. Grafts to the anterior tibial artery are preferably done following the anatomical course of the artery, bringing the graft to the popliteal fossa and then through the interosseous membrane into the anterior compartment. No postoperative anticoagulation is advisable. The role of sympathectomy is controversial. Blood flow through femorotibial bypasses has been measured as comparable to that of femoropopliteal bypasses, suggesting that the volume and reactivity of the vascular bed are also comparable (1). The longterm patency of femorotibial bypasses has been reported as superior to the femoropopliteal bypass (19). Since late closure of the bypass is not invariably followed by the reappearance of gangrene, measuring the success in terms of limb salvage rather than longterm patency seems more appropriate.

Summary

Twelve cases of femorotibial bypasses are reported. A success rate of 86% has been achieved. This report stresses the extent of gangrene which is still compatible with foot salvage. Total clinical and angiographic evaluation is necessary in the workup of any candidate for a major limb amputation.

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Cardiovascular Manifestations During Alcohol Withdrawal

BIJOY MEHTA, M.D., F.A.C.A. AND GEORGE SERENY, M.D., F.A.C.P., F.R.C.P.

Abstract

Seventy chronic alcoholics hospitalized for withdrawal from alcohol were examined for evidence of cardiac impairment. In order of frequency, sinus tachycardia, systolic and diastolic hypertension, presystolic gallop, systolic murmur and ventricular premature beats were found. The electrocardiogram was abnormal in 68% of the patients, showing sinus tachycardia, nonspecific T wave changes and occasional ventricular premature beats. All these changes were transitory and subsided after a few days of abstinence from alcohol.

Introduction

Chronic alcoholism is one of the major health hazards in modern time. Investigations into all areas of its complications are widespread. In the field of cardiology, the main interest seems to be focused on the acute and chronic effect of alcohol on myocardial function (5, 6, 8, 9). The fact that interruption of drinking can also lead to cardiac symptoms and signs is little known. It is important, however, for physicians to know that alcohol withdrawal can be responsible for cardiac abnormalities so they may avoid making erroneous cardiac diagnosis. The present paper describes the cardiac symptoms of alcohol withdrawal.

Materials and Methods

Seventy chronic alcoholic patients, in order of their admission to the hospital for detoxification from alcohol, were included in the study. There were 54 males and 16 females in the group; their ages ranged from 21 to 45 years. None of them had a history of any significant medical illness. History taking and physical examinations were performed on the first or second day of hospitalization. Questions were specifically asked to elict signs or symptoms of heart disease. Laboratory investigations in each patient included complete blood count, serum electrolytes, urea N, total serum proteins, albumin and globulin levels, bilirubin, calcium and phosphorus, magnesium and liver enzymes. Chest x-rays and 12-lead electrocardiograms (ECG) were taken in each patient.

Results

All the cardiac abnormalities are listed in Table I and Figures 1–3. Abnormal ECGs were seen in 47 patients (Table I, Fig. 3). We assume, that the pseudo-infarction pattern and the right bundle branch block seen in one patient, were incidental findings and unrelated to alcohol. No cardiomegaly or congestive changes were seen in the chest x-rays. The majority of abnormal cardiac findings subsided after two to four days of abstinence. The presystolic gallop heard in 17 patients on admission persisted in two patients for over three weeks. Seven patients had an ejection type of systolic murmur on admission and, in one patient, the murmur persisted over three weeks.

Discussion

When discussing the alcohol withdrawal syndrome, cardiac symptoms are usually not mentioned, although most of them as described in this study are present in the majority of alcoholic patients in withdrawal. The cardiac manifestations of withdrawal consist of sinus tachycardia, hypertension, presystolic gallop, systolic

TABLE I

Abnormal Cardiovascular Findings Within 24 to 48 Hours of Alcohol Withdrawal

Sinus tachycardia	42
Hypertension	28
Systolic > 160	
Diastolic > 95	
Presystolic gallop	17
Systolic murmur	7
ECG abnormalities	47

From the Alcoholism Program, Department of Medicine, Mount Sinai Services, City Hospital Center at Elmhurst, Elmhurst, N. Y. and Mount Sinai School of Medicine of The City University of New York, N. Y 10029.

P [illegible] requests should be sent to Dr. B. Mehta, Department of Me[illegible] Alcoholism Program, Mount Sinai Services, City Hospital C[illegible] urst, 79-01 Broadway, Elmhurst, N. Y. 11373.

TABLE II

EKG Abnormalities Within 24 to 48 Hours of Alcohol Withdrawal

Sinus tachycardia	42
Nonspecific T wave changes	12
Rare ventricular premature beats	2
Pseudo-infarction pattern	1
Right bundle branch block	1

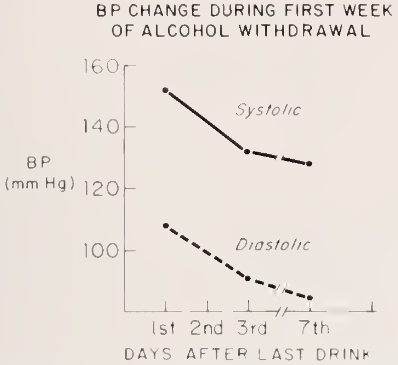

FIG. 1. Mean systolic and diastolic blood pressure changes in 70 patients during the first week of withdrawal from alcohol.

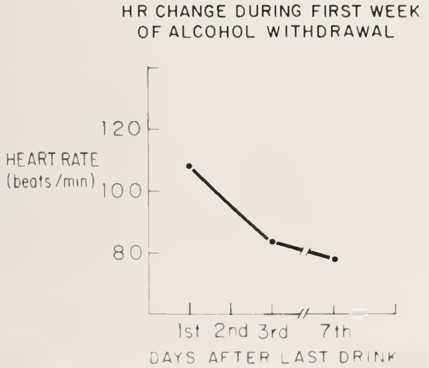

FIG. 2. Mean heart rate changes in 70 patients during the first week of alcohol withdrawal.

murmur and minimal ECG abnormalities. The symptoms seem to be transient and apparently are not caused by organic heart disease. A great deal of information is now available on the pathophysiology of alcohol withdrawal and the cardiac withdrawal symptoms seem to be the result of these abnormalities. It has been demonstrated that there is increased cathecolamine secretion in alcohol withdrawal (1–3, 8) and that the increased secretion can be blocked by adrenergic beta blockers. We believe sinus tachycardia, the transient systolic murmur, and the presystolic gallop were caused by increased cathecolamine secretion in our patients.

The electrocardiographic abnormalities were diphasic or inverted T waves and sinus tachycardia (Figs. 2, 3). It has been shown that repolarization abnormalities are also connected to increased cathecolamine levels and to altered cell membrane permeability and/or decreased intracellular potassium (5, 7). It has been suggested that these ECG abnormalities are not caused by organic heart disease and that they subside within 48 to 72 hours of hospital admission.

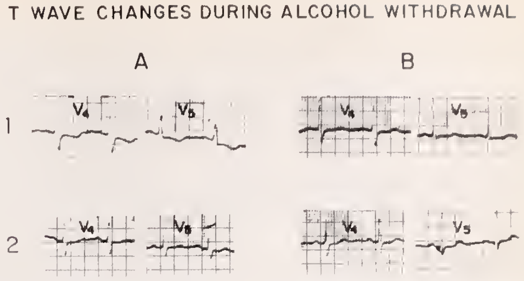

FIG. 3. A) T wave changes in two alcoholic patients (1 and 2) 24 hours after their last drink. B) T wave abnormalities returning towards normal in the same two patients 72 hours after admission.

The most important cardiovascular abnormality is the hypertension found in a high percentage of patients in withdrawal (Fig. 1). In chronic alcoholics, hypertension can be caused by both excessive drinking and alcohol withdrawal (10). The blood pressure may remain elevated from a few days to several weeks. In the majority of the patients, the blood pressure returns to normal without any hypertensive therapy (Fig. 1). Hypertension in chronic alcoholics is very difficult to treat unless the patient is willing to remain abstinent. If the patient continues to drink, the blood pressure is almost always unresponsive to drug treatment, partly because of noncompliance and partly because drug efficacy is reduced in the presence of alcohol.

Knowing that such a well-defined group of cardiac abnormalities exists in the majority of patients in alcohol withdrawal, will avoid erroneous diagnosis and will focus on the correct one – chronic alcoholism.

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Acute Polymyositis Caused by Sarcoidosis: Report of a Case and Review of the Literature

JACK N. ALPERT, M.D., ARCHIE EDWARD GROFF, M.D., FRANK O. BASTIAN, M.D.,
AND MORTON A. BLUM, M.D.

Abstract

A case of sarcoidosis manifested by an acute myositis is described along with a review of the literature. The patient was a 15-year-old girl who had fever, myalgia, dyspagia, dysarthria, and mild proximal muscle weakness. Creatine phosphokinase and aldolase were markedly elevated. Muscle biopsy showed noncaseating granulomatous inflammation typical of sarcoidosis. There was a prompt response to steroid therapy.

Although sarcoidosis has protean clinical manifestatons, myopathy is rare. Muscular involvement is common but usually asymptomatic (1, 2). Symptomatic forms include palpable nodules, myopathy with other organ involvement and pure myopathy (3). The myopathy is typically chronic, slowly progressive, often associated with wasting and resembling muscular dystrophy or chronic polymyositis. Rare cases have presented with acute myositis with only eight cases documented in the literature. We are reporting a fifteen-year-old girl who had an acute onset of myositis, simulating acute polymyositis but which proved on muscle biopsy to be sarcoidosis myopathy.

Case Report

A 15-year-old white girl was admitted to St. Luke's Episcopal Hospital because of fever of an unknown origin. Eight days prior to admission she developed left shoulder pain, edema and swelling of the jaws, fever and sore throat. Although a throat culture was negative, she was treated with penicillin without benefit. The day after admission she complained of thigh pain and difficulty lifting her legs. Two days after admission, she developed dysarthria and dysphagia.

Past medical history was unremarkable except for infectious mononucleosis two years prior.

General physical examination revealed a young girl in mild distress with a blood pressure of 135/50, pulse 100, and temperature 103. The pharynx was mildly injected, and there was facial swelling especially in the region of the parotid glands. The left shoulder was warm and erythematous with pain present on shoulder abduction.

Neurologic examination five days after admission revealed dysarthria with a nasal quality, tender thigh muscles to palpation and variable mild weakness of iliopsoas.

Laboratory data included a hemoglobin of 12.8 grams, white blood cell count of 10,000 with a normal differential. FTA-ABS was nonreactive. Sedimentation rate was 48. Rheumatoid factor, antinuclear antibody and protein electrophoresis were normal. Calcium, phophorus, blood urea nitrogen, uric acid, cholesterol, thyroid and liver function studies were normal. Febrile agglutinins were negative. CSF was clear, colorless, under normal pressure with a protein of 24 mg% and sugar of 60 mg%. Urine for myoglobin was negative. Creatine phosphokinase was 1650 and 920 initially and returned to normal levels as an outpatient. Aldolase was 57.3 and 56.5 prior to initiation of treatment. Electrocardiogram and chest x-ray were normal. Blood, urine, CSF and cervical cultures were normal. PPD was negative. A Tensilon test resulted in an equivocal improvement in speech. Bone marrow biopsy showed a normal cellular marrow with myeloid hyperplasia and slight eosinophilia.

A biopsy of the left deltoid muscle was performed on the seventh day of hospitalization (Fig. 1). The specimen showed no characteristic features on gross examination but histologic sections showed extensive fibrous thickening of the connective tissue septae with massive inflam-

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From the Departments of Neurology, Medicine, and Pathology, St. Lukes Episcopal Hospital, Houston, Tx.

Requests for reprints should be sent to Jack N. Alpert, M.D., 910 Hermann Professional Building, Houston, Tx. 77030.

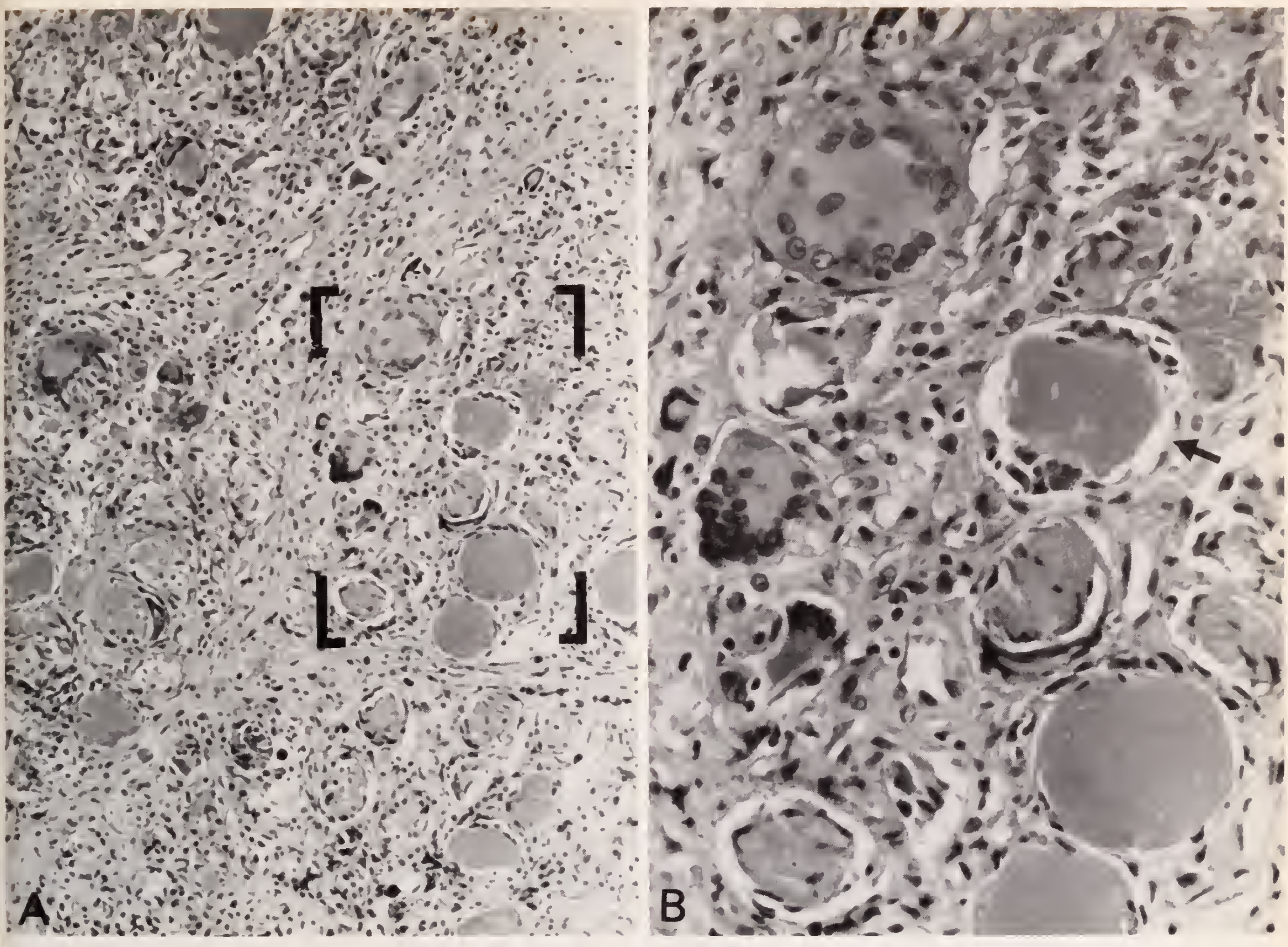

FIG. 1. A) Skeletal muscle biopsy showing fibrous thickening of connective tissue septae with marked inflammatory infiltrate. H & E original magnification × 63. B) Higher magnification of area bracketed in A showing noncaseating granulomatous inflammation with prominent Langhans giant cells. Note degenerating muscle fibers (arrow). H & E original magnification × 400.

matory infiltration. This tissue reaction consisted entirely of noncaseating granulomatous inflammation with numerous Langhans giant cells and epitheloid histocytic proliferation along with minimal lymphocytic response. This inflammatory process extended into the adjacent skeletal muscle bundles which showed focal fiber degeneration. No histochemical abnormality was discovered. A sample examined by electron-microscopy showed no specific pathologic changes. Examination of the tissues by special stains and at the ultrastructural level revealed no microorganisms.

The patient was treated with prednisone 60 mg per day. Swallowing, speech and muscle strength returned to normal in five days. Intermittent weakness of iliopsoas associated with tendernesss of all thigh muscles occurred for approximately three months. These symptoms required low dose, alternate day prednisone therapy. The patient is now asymptomatic.

Discussion

Muscular involvement by sarcoidosis has been divided into three categories – asymptomatic, palpable nodules, and myopathy (3). Asymptomatic granulomatous inflammation is common as severe histologic changes may occur without myopathy (1, 2). Myopathy is rare. In one comprehensive study of muscular involvement, three cases were discovered out of a total of 800 patients with sarcoidosis (4). A review of the literature yielded a total of 52 patients reported to have myopathy. This myopathy has been divided into two forms, pure myopathy and myopathy with other organ involvement. A distinction has not usually been made between the types of clinical presentation, namely the chronic progressive myopathy and the acute myositis.

The clinical picture of the myopathy is generally characterized as a chronic, slowly progressive myopathy often resembling muscular dystrophy or chronic polymyositis (3–14). It is late in onset with an average age reported to be 50 (1, 3, 8). Most of the patients are postmenopausal women (3, 5). Atrophy is a frequently described feature along with proximal muscular weakness (1, 3, 8).

Our patient exhibited an entirely different clinical picture. She was 15-years old with an acute onset of a febrile illness, parotid enlargement and sore muscles. The acutely symptomatic muscular involvement was mainly pharyngeal and soft palate, and less so shoulder and pelvic girdle.

A review of the literature revealed eight other cases of an acute inflammatory myopathy (4, 7, 12–15). Occasionally, this was only a transient phase as part of a chronic progressive myopathy. Features of these patients included fever, night sweats, adenopathy, tachycardia, arthralgia, myalgia muscle tenderness, and variable muscle weakness particularly involving shoulder and pelvic girdle and rarely pharynx. Cardiac involvement has occurred and been fatal (8, 12).

Laboratory data has not been striking in most reports. Elevated gamma globulin is the most consistent finding (3, 9, 12, 13). Hypercalcemia, increased aldolase and sedimentation rate and creatinuria have been observed (3, 9, 11–13). The highest sedimentation rate reported was 38. Our patient had marked elevation of CPK, 1650 and 920, and aldolase, 56.5 and 57.3, but globulins were normal. Sedimentation rate was 48.

The histologic sections of this patient's muscle biopsy showed noncaseating granulomatous inflammation. The absence of caseating necrosis would appear to negate the possibility of certain specific inflammatory conditions such as tuberculosis or fungus infection, a supposition reinforced by negative special stains for microorganisms. A rare giant cell may be found in acute polymyositis but this cell is usually of the foreign body type and true granulomatous inflammation has not been described in that condition. The tissue reaction seen in this biopsy was characteristic of sarcoidosis.

Steroid treatment has been proposed, but there is conflicting evidence regarding its efficacy. Four patients with an acute myositis responded to steroids. Two were not treated, one refused treatment and one improved spontaneously. Our patient responded promptly and dramatically. Of the patients with a chronic myopathy reported in the literature, there was a beneficial response to steroids in 20 of 31 treated patients (5).

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Biliary Obstruction Associated with Chronic Pancreatitis: Surgical Approaches

UNSUP KIM, M.D., F.A.C.S., HANYU SHEN, M.D., AND JOSE ROMEU, M.D.*

Because of the intimate anatomical relationship between the distal portion of the bile duct and the head of the pancreas, transient hyperbilirubinemia is a frequent occurrence during the course of acute pancreatitis (1–3). Chronic or persistent biliary obstruction, however, is rarely associated with chronic relapsing pancreatitis, and results from encasement of the bile duct with dense fibrotic changes of the pancreas, or is caused by the mechanical compression of the bile duct by unresolving pseudocyst of the pancreatic head.

Sustained high levels of serum amylase and alkaline phosphatase in patients with chronic pancreatitis should raise suspicion of mechanical obstruction with bile duct stricture as the cause. Hepatitis, calculous or malignant biliary obstruction have to be excluded. To this end, transhepatic cholangiogram and endoscopic retrograde cholangiopancreatogram (ERCP) are equally effective means of demonstrating both the degree and length of bile duct involvement in stricture formation. ERCP can give additional information regarding pathologic changes of the pancreatic duct and the absence or presence of pseudocyst of the pancreas.

While no surgical treatment is indicated in a transient biliary obstruction associated with acute pancreatitis, surgical relief of biliary obstruction is required for organic stricture formation of the bile duct caused by chronic pancreatitis to prevent recurrent cholangitis and secondary biliary cirrhosis.

The purpose of this report is to present five cases of biliary obstruction associated with chronic pancreatitis with or without pseudocyst of the pancreatic head, and to illustrate surgical approaches to effectively bypass the biliary obstruction.

Case Reports

Case 1

A 44-year-old white female was admitted to Elmhurst General Hospital on June 12, 1977 because of increasing jaundice and pruritus. She had a cholecystectomy and common bile duct exploration with T-tube drainage in 1967 for acute alcoholic pancreatitis. The postoperative course was complicated by prolonged, profuse drainage of bile from the T-tube and T-tube cholangiogram revealed a marked narrowing of the distal common bile duct which was thought to be caused by subacute pancreatitis. Thoracic duct annulation resulted in improvement of pancreatitis. Subsequently, the T-tube was removed and she was discharged home.

She remained asymptomatic despite continued abuse of alcohol. She returned to the hospital in April of 1976 with clinical symptoms and signs of complete upper jejunal obstruction and severe dehydration. A small bowel series confirmed the clinical impression. At laparotomy, an obstruction of the duodenojejunal junction from severe fibrotic adhesions secondary to chronic pancreatitis was found. A duodenojejunostomy resulted in an uneventful recovery. Multiple biopsies were taken from the pancreas which failed to show evidence of neoplasm. She was discharged home on anticoagulant therapy for thrombophlebitis of the lower extremities, which she had developed postoperatively. The patient was readmitted to the hospital in June 1977 because of increasing jaundice and pruritus. Serum bilirubin was 9.4 mg%, serum alkaline phosphatase was over 1,000 units, and serum amylase was 108 dye units. Another abnormal laboratory finding was mildly elevated fasting blood sugar. A transhepatic cholangiogram showed near complete obstruction of the distal common bile duct with marked dilatation of entire biliary system (Fig. 1).

On June 16, 1977, the patient underwent choledochojejunostomy in Roux-en-y fashion (Fig. 2), with an un-

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From the Departments of Surgery and *Medicine, City Hospital Center at Elmhurst, Elmhurst, N.Y.

Requests for reprints should be sent to Unsup Kim, M.D., Director, Department of Surgery, City Hospital Center at Elmhurst, 79-01 Broadway, Elmhurst, New York 11373.

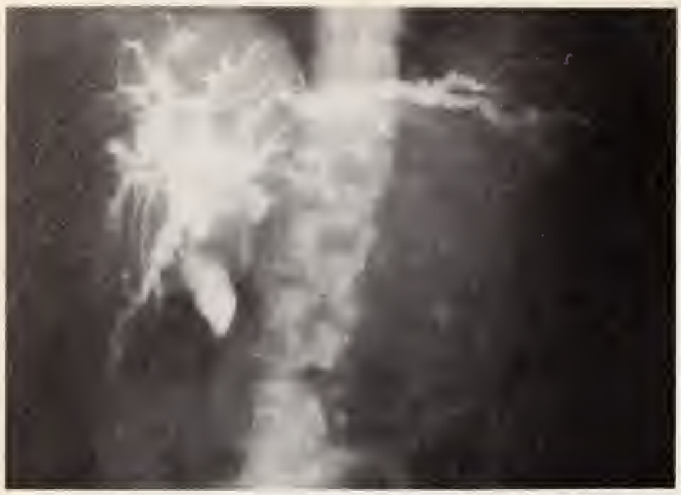

FIG. 1. Transhepatic cholangiogram showing a stricture of the distal common bile duct with marked dilatation of biliary tree.

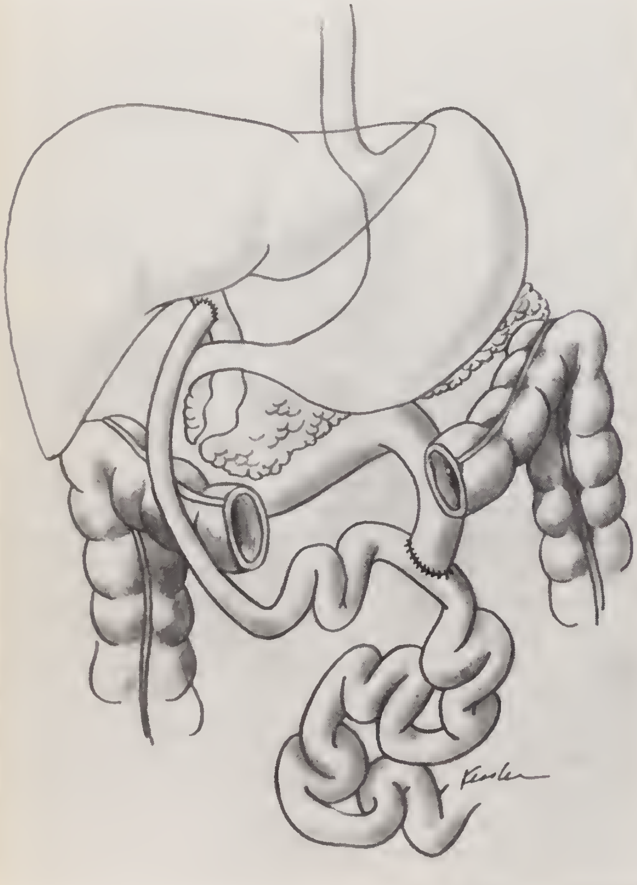

FIG. 2. Diagram shows Roux-en-y choledochojejunostomy.

eventful postoperative course. The obstruction of the common bile duct was from severe fibrotic changes in the head of the pancreas, biopsy of which showed chronic inflammation. She remains asymptomatic.

Case 2

A 43-year-old chronic alcoholic black male was admitted to Elmhurst General Hospital on August 3, 1976 with a five-month history of abdominal pain, nausea, and vomiting. Physical examination showed a markedly dehydrated, disoriented black male with evidence of recent weight loss. The abdomen was not distended. A tender, poorly defined mass was palpated in the right upper quadrant of the abdomen. Abnormal laboratory findings included serum bilirubin of 17.4 mg%, alkaline phosphatase of 1,050 units, and serum amylase of 400 dye units. He responded to intravenous hydration and supportive therapy.

An upper gastrointestinal (GI) series showed a widen-

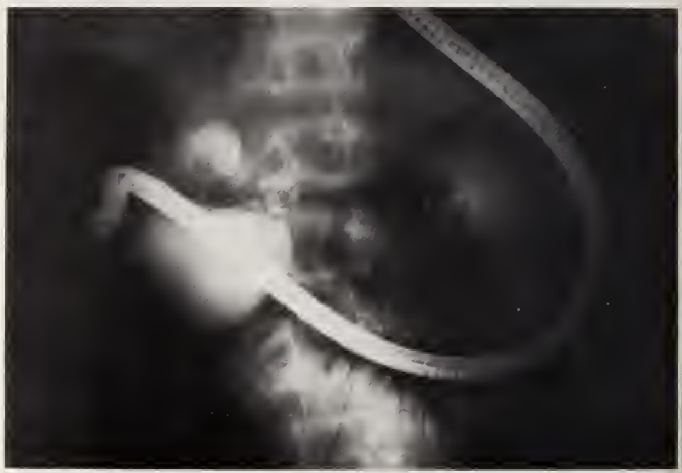

FIG. 3. ERCP showing a pseudocyst in the head of the pancreas.

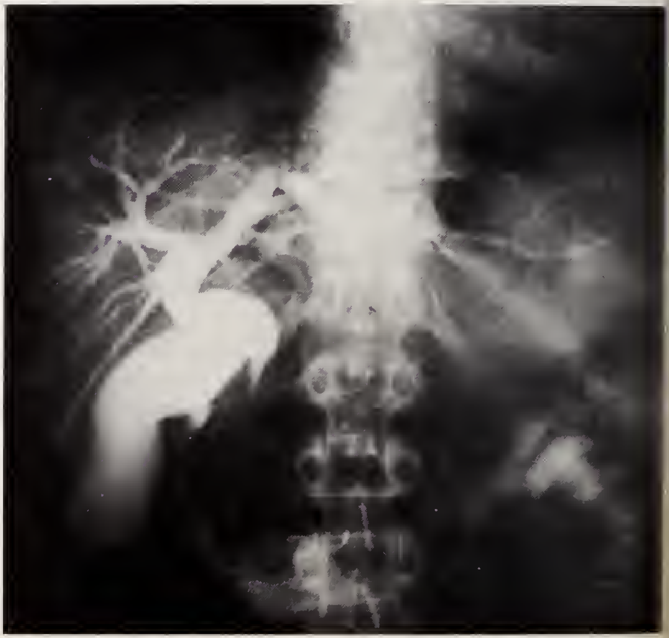

FIG. 4. An operative cholecystocholangiogram showing a long stricture formation of the distal bile duct with dilatation of the proximal bile duct.

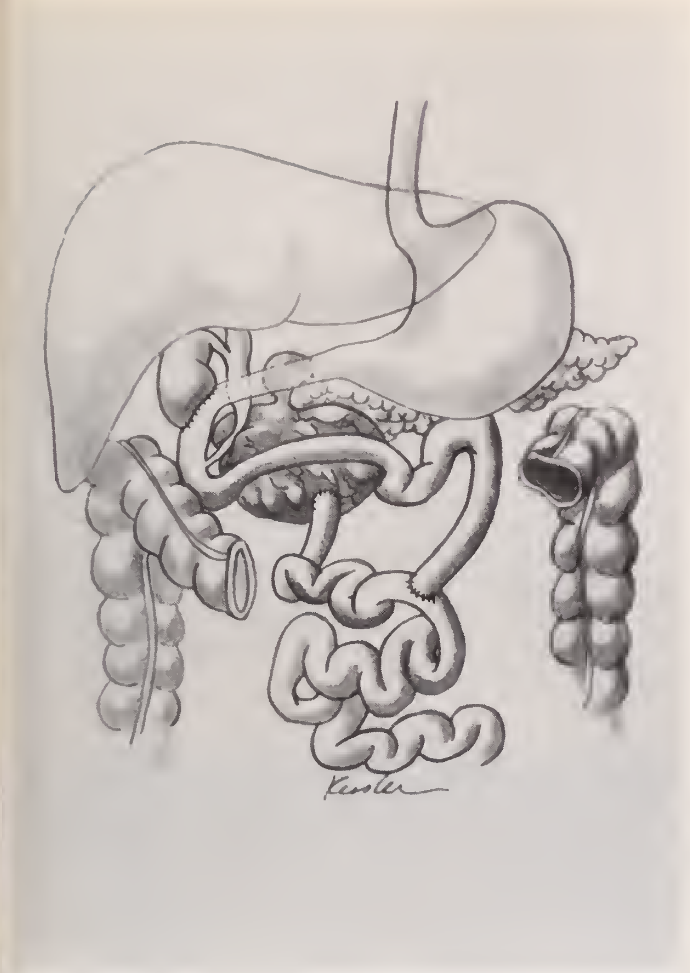

FIG. 5. Shows cholecystoduodenostomy and Roux-en-y cystojejunostomy.

ing of the duodenal sweep. Sonogram revealed a cystic mass in the head of the pancreas. ERCP showed a cyst in the head of the pancreas. Neither the bile duct nor the pancreatic duct was visualized (Fig. 3).

Laparotomy on August 23, 1976 revealed chronic pancreatitis with a pseudocyst of the pancreatic head, and operative cholecystocholangiogram showed a marked narrowing of the long segment of the distal bile duct (Fig. 4). Cholecystoduodenostomy and pseudocystojejunostomy in Roux-en-y fashion were performed (Fig. 5). The postoperative course was uneventful, and the patient remains asymptomatic.

Case 3

A 72-year-old Hispanic male was admitted to Elmhurst General Hospital on August 8, 1977 with a two-month history of right upper quadrant mass and a weight loss of about 35 pounds. Past medical history was noncontributory. No history of alcoholic abuse was elicited. A distinct mass could be palpated in the right upper quadrant of the abdomen below the costal margin, that had all the characteristics of a distended gallbladder.

Abnormal laboratory findings were serum amylase of 732 dye unit on admission, serum bilirubin of 1.8 mg%, and alkaline phosphatase of 400 units. Serum bilirubin progressively rose to 21.9 mg% with predominantly direct component. Intravenous pyelogram, barium enema, and liver scan were normal. Sonogram showed a distended gallbladder, and a mass in the head of the pancreas. A transhepatic cholangiogram showed a long segment of narrowing in the distal common duct and a distended gallbladder. A clinical diagnosis of carcinoma of the head of the pancreas was entertained. Laparotomy on August 25, 1977 revealed a markedly dilated common duct. A firm mass was felt at the head of the pancreas. Biopsy of the lymph nodes around the common duct and peripancreatic regions demonstrated inflammation and no evidence of tumor. Transduodenal needle biopsy of the pancreatic mass showed pancreatitis.

Choledochojejunostomy in Roux-en-y fashion, and gastrojejunostomy and vagotomy were performed, the

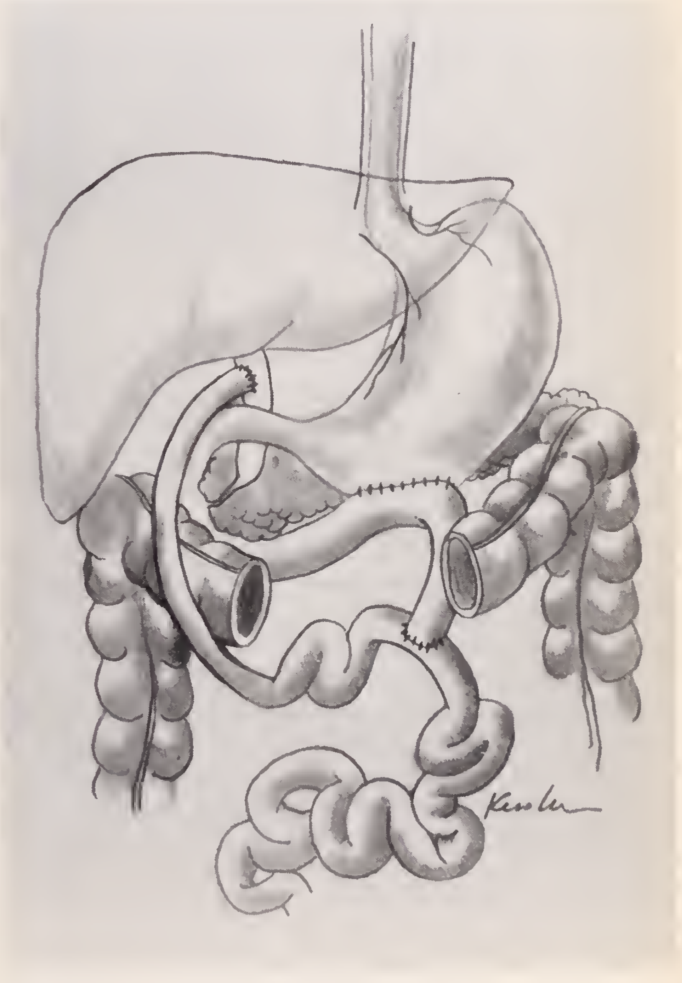

FIG. 6. Shows choledochojejunostomy in Roux-en-y, vagotomy, and gastrojejunostomy.

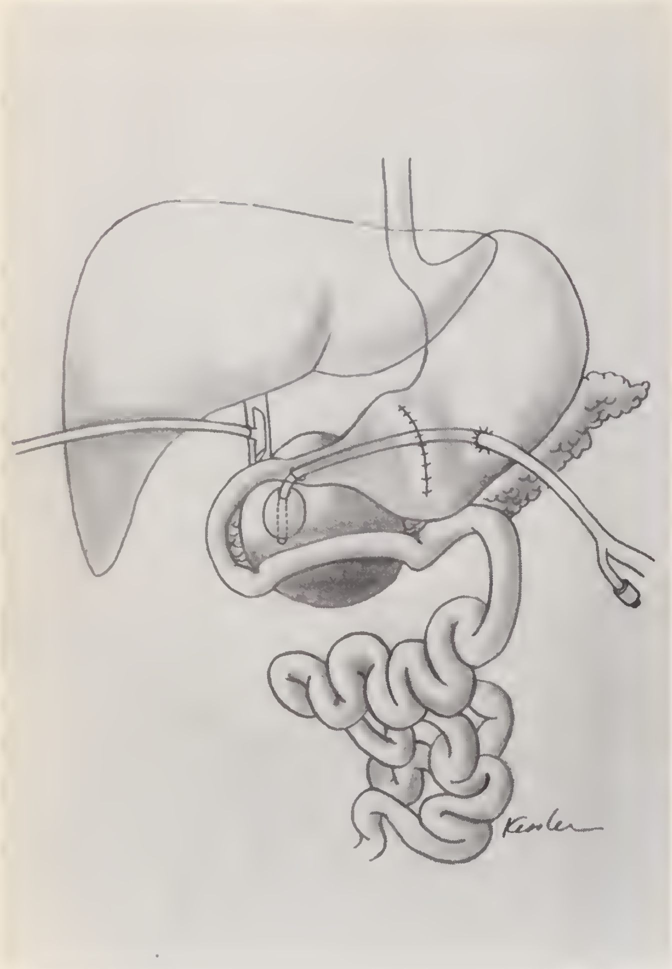

FIG. 7. Shows cystoduodenostomy, pyloroplasty, and tube gastrostomy.

latter procedure because carcinoma of the head of the pancreas could not be completely ruled out (Fig. 6).

The postoperative course was uneventful except for pulmonary embolism, which was successfully treated with anticoagulant therapy. The patient gained weight and the jaundice completely subsided.

On September 4, 1978, the patient was readmitted to the hospital with an acute onset of abdominal pain, and clinical signs of septic peritonitis and shock. Emergency laparotomy revealed generalized fecal peritonitis from free perforation of sigmoid diverticulitis. Excision of the inflamed sigmoid with double barreled colostomy was performed. No evidence of tumor was found in the pancreas. Previously constructed choledochojejunostomy was intact. The postoperative course, however, was steadily downhill, and the patient expired five days after surgery.

Case 4

A 48-year-old white female was admitted to Elmhurst General Hospital with painless jaundice and pruritis on June 11, 1976. She was a known alcoholic with a significant psychiatric history.

The admission serum bilirubin was 18 mg%, predominantly of direct component and alkaline phosphatase was over 600 units. Serum amylase was normal. Liver enzymes were normal. An upper GI series showed a retroduodenal mass, consistent with enlarged pancreatic head or cyst. ERCP showed a large cystic lesion in the region of the head of the pancreas. Common bile and pancreatic ducts were otherwise normal.

Exploratory laparotomy on July 6, 1976 disclosed a distended gallbladder containing stones, and a dilated common bile duct measuring approximately 1.5 cm. without evidence of stones. A pseudocyst was present at the head of the pancreas that contained about 200 cc of uninfected pancreatic secretion. This cyst was the cause of the biliary obstruction. A cholecystectomy and T-tube drainage of the common bile duct, and pseudocystoduodenostomy through a gastroduodenostomy were performed. A tube was inserted into the cyst through the anastomosis and was brought out through the stomach

FIG. 8. IVC showing dilated common bile duct with calcifications in the head of the pancreas.

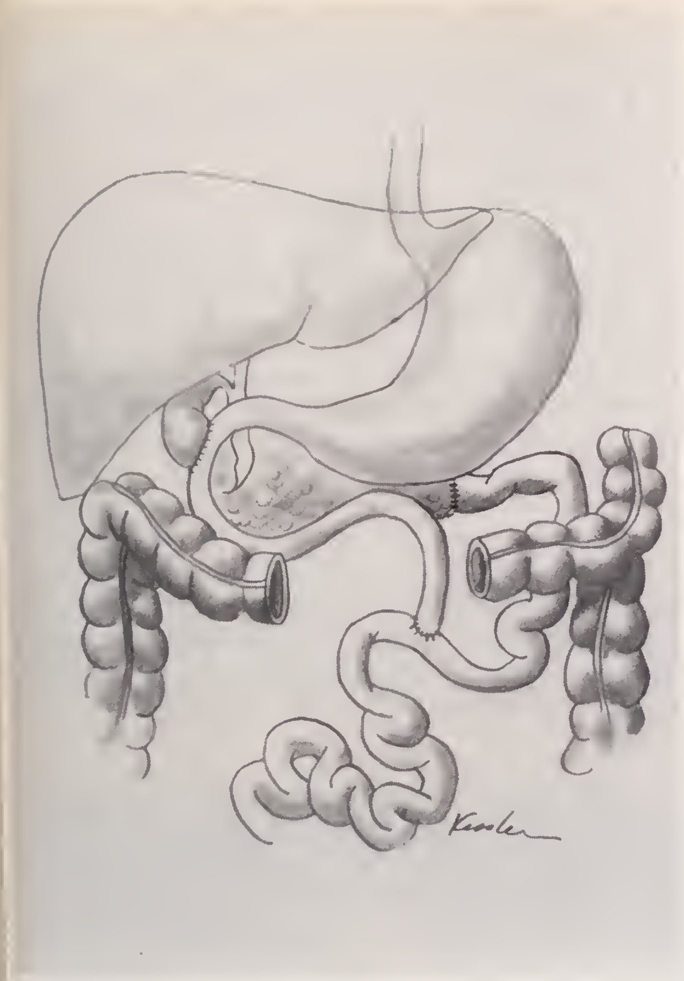

FIG. 9. Shows cholecystoduodenostomy, Roux-en-y pancreaticojejunostomy.

as a gastrostomy. The gastroduodenotomy was closed to form a pyloroplasty (Fig. 7).

The postoperative course was uneventful, and the patient was discharged home. She remained asymptomatic, except for a manic depressive reaction, for which she was readmitted to a psychiatric ward.

Case 5

A 28-year-old black male was admitted to Elmhurst General Hospital with right upper quadrant abdominal pain radiating to the back and with associated nausea and vomiting. The patient was a known chronic alcoholic with documented episodes of pancreatitis in the past.

A positive physical finding at the time of admission was an indication of localized peritonitis in the right upper quadrant of the abdomen. Abnormal laboratory indings included serum bilirubin of 2.7 mg% which rose to 9.0 mg% and a marked elevation of serum amylase up to 530 units. Plain abdominal x-ray showed diffuse calcifications in the region of the head of the pancreas. Subsequent intravenous cholangiogram showed a dilated bile duct without evidence of stones (Fig. 8). Exploratory laparotomy on January 19, 1978 showed a dilated common bile duct, normal gallbladder, and diffuse fibrocalcific changes of the pancreas. A cholecystoduodenostomy and distal pancreatectomy with pancreaticojejunostomy were performed (Fig. 9).

The postoperative course was uneventful, and the patient remains asymptomatic except for episodes of abdominal pain related to resumed abuse of alcohol.

Comment

The fixed stricture formation of the common bile duct is a rare but well established complication of chronic recurrent pancreatitis. Advances in endoscopic retrograde cholangiopancreaticography and transhepatic cholangiography have contributed to more frequent and early diagnosis of this condition. A variety of surgical procedures are used by different surgeons to effectively bypass the obstructed bile duct with satisfactory long-term results – cholecystoduodenostomy, cholecystojejunostomy, choledochojejunostomy, and Whipple's operation (2, 4, 5). Selection of the procedure depends primarily on the availability of the gallbaldder, the size of the common bile duct, absence or presence of concomitant pseudocyst, and other local conditions.

Cholecystoduodenostomy is technically simple and provides a good long-term result. In one case reported here, biliary enteric bypass was added to the internal drainage of the pseudocyst to secure relief of biliary obstruction, although the major cause of it seemed to be the pseudocyst.

Biopsy of the peripancreatic nodes or the pancreas itself is important to rule out concomitant malignant tumor.

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Maternal Death Due to Lupus Pneumonitis in Pregnancy

WILLIAM H. AINSLIE, JR., M.D., KLARA BRITT, M.D., AND, JASMIN A. MOSHIPUR, M.D.

Abstract

An interesting case report of postpartum maternal mortality secondary to lupus pneumonitis is presented. The pathologic findings are described, and several photographs are included for illustration. A brief discussion of the effects of pregnancy on the state of the disease is also included.

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease punctuated by spontaneous exacerbation and remission. The etiology is unknown, but the widespread inflammatory response appears to be initiated by DNA and anti-DNA complexes. Many organ systems are involved that lead to a myriad of clinical manifestations.

Symptoms most frequently involve the skin or the joints, appearing as a malar rash, Raynaud's phenomenon, or polyarthralgia. Renal disease complicates the picture in half of the cases and is the determining feature in the outcome of the disease. There are three pathologic renal states: focal proliferative nephritis, membranous lupus, and diffuse lupus nephritis. The latter has the worst prognosis (1).

Systemic lupus erythematosus is of particular importance to the obstetrician because it is a disease striking primarily the female of child bearing age. The disease can easily be confused with common obstetric problems such as hypertensive disorders of pregnancy. It also has a direct effect on the outcome of a pregnancy. Many studies report increased fetal wastage with spontaneous abortion, premature labor, and stillbirth being increased by one third (2–8). Even with advances in disease management brought about by the use of corticosteroids, reduction in fetal loss has not been observed (4, 5, 7, 8). More important, perhaps, is the effect of pregnancy on the disease itself.

In the case presented here, the patient demonstrates a particularly fulminant form of lupus erythematosus. The events came in quick succession, and the outcome was unique. A search of the literature revealed only one similar case, and it was reported at the time of the occurrence of the present case (9).

Case Report

The patient was a 21-year-old primigravida of Mexican descent with a last menstrual period on October 10, 1977. She came to the prenatal clinic at 34-weeks gestation by dates. Her past medical, surgical, and family history was noncontributory except for her history of rheumatoid arthritis. Prior to becoming pregnant in October 1977, the patient had noticed increased stiffness in her wrists and interphalangeal joints associated with the loss of sensation in her finger tips. In December 1977, while still in Mexico, a diagnosis of rheumatoid arthritis had been made based upon clinical findings and unknown laboratory data including a positive rheumatoid factor. From this point until her clinic visit in June she had received no prenatal care. She had moved to New York City in March. Her previous symptoms had resolved along with a nondescript rash on her arms and legs that had developed during January.

When the patient came to our clinic for the first time at 34-weeks gestation, she was admitted for premature labor. Her blood pressure was 120/70 mm Hg with a pulse of 80 bpm, and her physical exam was unremarkable except for 2+ pedal edema. Sonographic biparietal measurement correlated with 34-weeks gestation. Labor was suppressed with diazoxide (300 mg IV over 20 minutes). Laboratory findings revealed a hemoglobin of 7.5 gm%, a WBC of 3400/mm^3, and a platelet count of 150,000/mm^3. The SMA-6 and 12 were normal except for the following: urea nitrogen 31 mg/100 ml, creatinine 1.1

From the Department of Obstetrics-Gynecology and Pathology, Mount Sinai School of Medicine, New York, N.Y.

Requests for reprints should be sent to Dr. William H. Ainslie, Jr., 73 Amboy Ave., Metuchen, New Jersey.

mg/100 ml, albumin 2.3 gm/100 ml, and calcium 7.4 mg/100 ml. Urine analysis showed 4+ proteinuria, moderate blood, 20–30 WBC's, 30-40 RBC's, and moderate epithelial cells. Urine culture was negative. The urinary protein was 4.7 gm/24 hrs with a cretatinine clearance of 80 cc/min. The coagulation profile consisted of the following: prothrombin time normal, partial thromboplastin time normal, fibrinogen 220 mg%, fibrin split products positive. Chest x-ray and ECG were normal. A positive LE test along with a decreased serum complement (C3) level (12 mg%) supported our diagnosis of SLE.

The patient was jointly managed by the Renal and Obstetric Services. The plan was to control the disease process with intravenous steroids (dexamethasone 3 mg every six hours and to maintain the pregnancy as long as possible. Twice weekly serum estriols and human placental lactogen levels along with weekly nonstress tests were performed. Daily SMA-6, SMA-12, CBC, urine analysis, and 24 hr urine for protein and creatinine along with weekly serum complement levels were drawn to follow the state of the disease.

Day 7: The patient showed no signs of successful response to the steroids. The patient was less alert with 4+ pedal edema and anasarca. Laboratory data on blood serum revealed urea nitrogen 40 mg/100 ml, creatinine 1.3 mg/100 ml, albumin 1.3 gm/100 ml, and calcium 8.4 mg/100 ml. 24 hr urine for protein was 7.3 gms with a creatine clearance of 70 cc/min. The coagulation profile remained unchanged.

Day 8: A low grade fever of 99.2 F developed accompanied by a pulse of 100 bpm and a respiratory rate of 30 bpm. Scattered rales were noted bilaterally in the lower lobes. A chest x-ray confirmed bilateral lobe infiltrates with a small amount of fluid in the angles. Blood gases revealed a PH of 7.43, PO2 85 mm Hg, and PCO2 23 mm Hg. The patient was started on intravenous cephalothin with a diagnosis of pneumonia.

Day 9: The patient went into labor, and a primary low flap vertical cesarean section for fetal transverse lie was performed. A viable male infant was delivered with a one minute apgar of eight and a five-minute apgar of ten. The patient tolerated the procedure well, and postoperatively, she continued on intravenous cephalothin and started on intravenous hydrocortisone (100 mg Q6H).

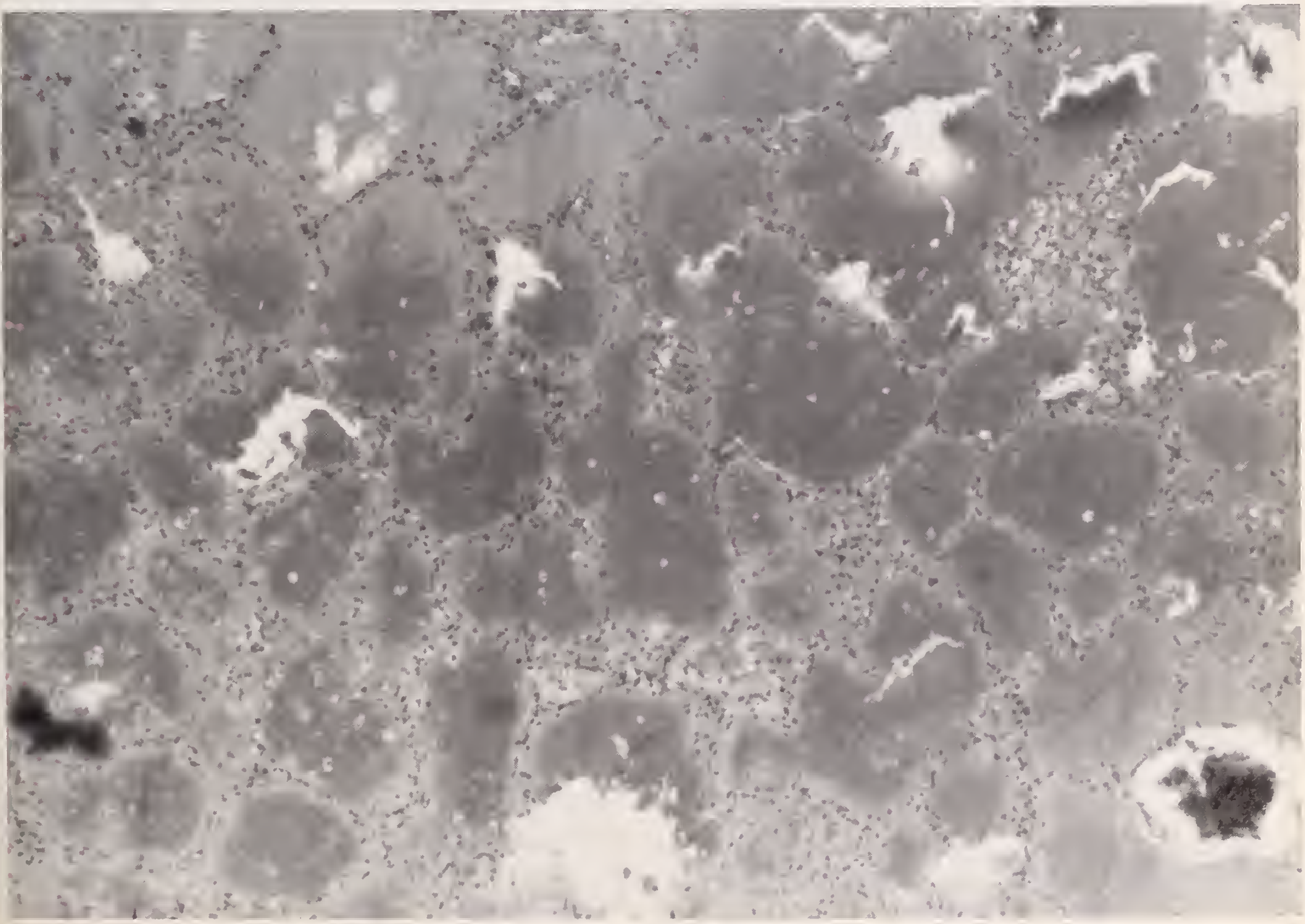

FIG. 1. Lung with diffuse intra-alveolar hemorrhages.

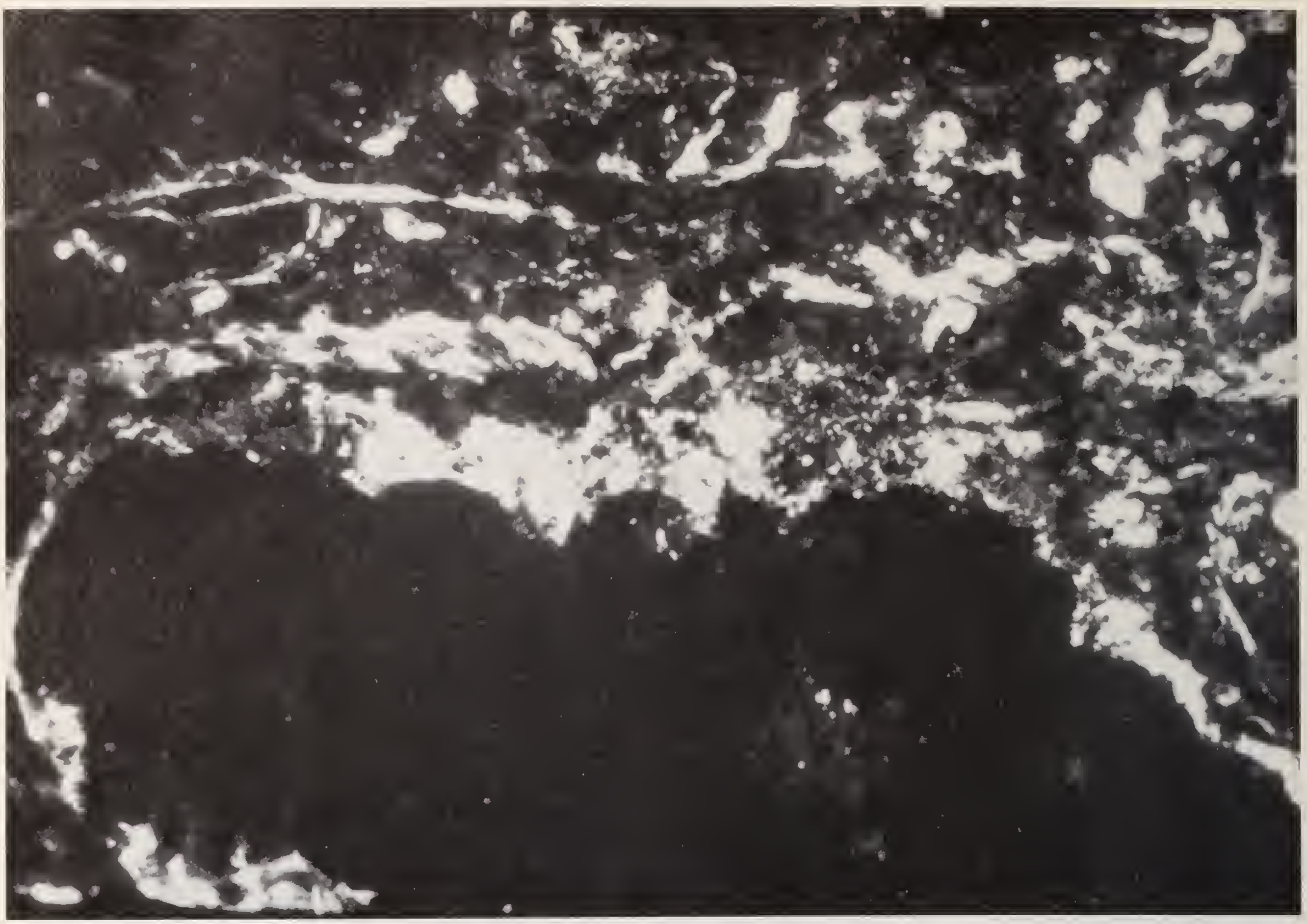

FIG. 2. Immunofluorescence demonstrating IgG in alveolar wall. *Special thanks to Dr. Michael Gerber for this photograph.

Postoperative day 2: Tachycardia, tachypnea, and dyspenea developed associated with hemotysis. Rales were elicited in the lower third of each lung field. Repeat chest x-ray revealed bilateral diffuse alveolar infiltrates in the lower lung fields and cardiac shadow enlargement. ECG revealed low voltage without acute change. Blood gases showed a PH of 7.33, PO2 48.7 mm Hg, and PCO2 26.6 mm Hg. The lung scan was consistent with congestive heart failure while the Echo cardiogram revealed a small posterior pericardial effusion but no functional defect. Pneumonia, mild cardiac failure, and cardiac effusion were diagnosed, but pulmonary embolism could not be ruled out. The patient was then transferred to the medical service.

Postoperative day 3: Despite satisfactory diuresis secondary to the use of diuretics, the patient's status remained unchanged. Basilar rales, tachycardia, tachypnea, and dyspnea persisted. The abdomen became softly distended with decreased bowel sounds. The WBC rose to 14,000 mm^3 with a shift to the left, and methylprednisolone and tobramycin were started.

Postoperative day 4: The patient was transferred to the intensive care unit. Her respiratory status stabilized only after intubation on 40% O2 with positive end-expiratory pressure. Blood serum data showed urea nitrogen 74 mg/100 ml, creatinine 1.8 mg/100 ml, albumin 2.2 mg/100 ml, and calcium 8.3 mg/100 ml. Twenty-four hr urinary protein was 2 gms. A spinal tap revealed clear fluid, unremarkable except for slightly increased total protein (68 mg/100 ml). Blood pressure remained stable at 120/70 mm Hg; however, the pulse rose to 110 bpm. Examination of the hematocrit revealed a drop from 30 ml/100 ml to 21 ml/100 ml over the previous 48-hour period. The coagulation profile remained normal, but blood tinged sputum and absent bowel sounds persisted. The lungs as well as the abdomen were considered as sources for internal bleeding. Fever continued with a spike of 101 F°.

During the following three-day period the patient's condition continued to deteriorate. She had several grand mal seizures and became comatose. Blood serum urea nitrogen, creatinine, and albumin remained unchanged.

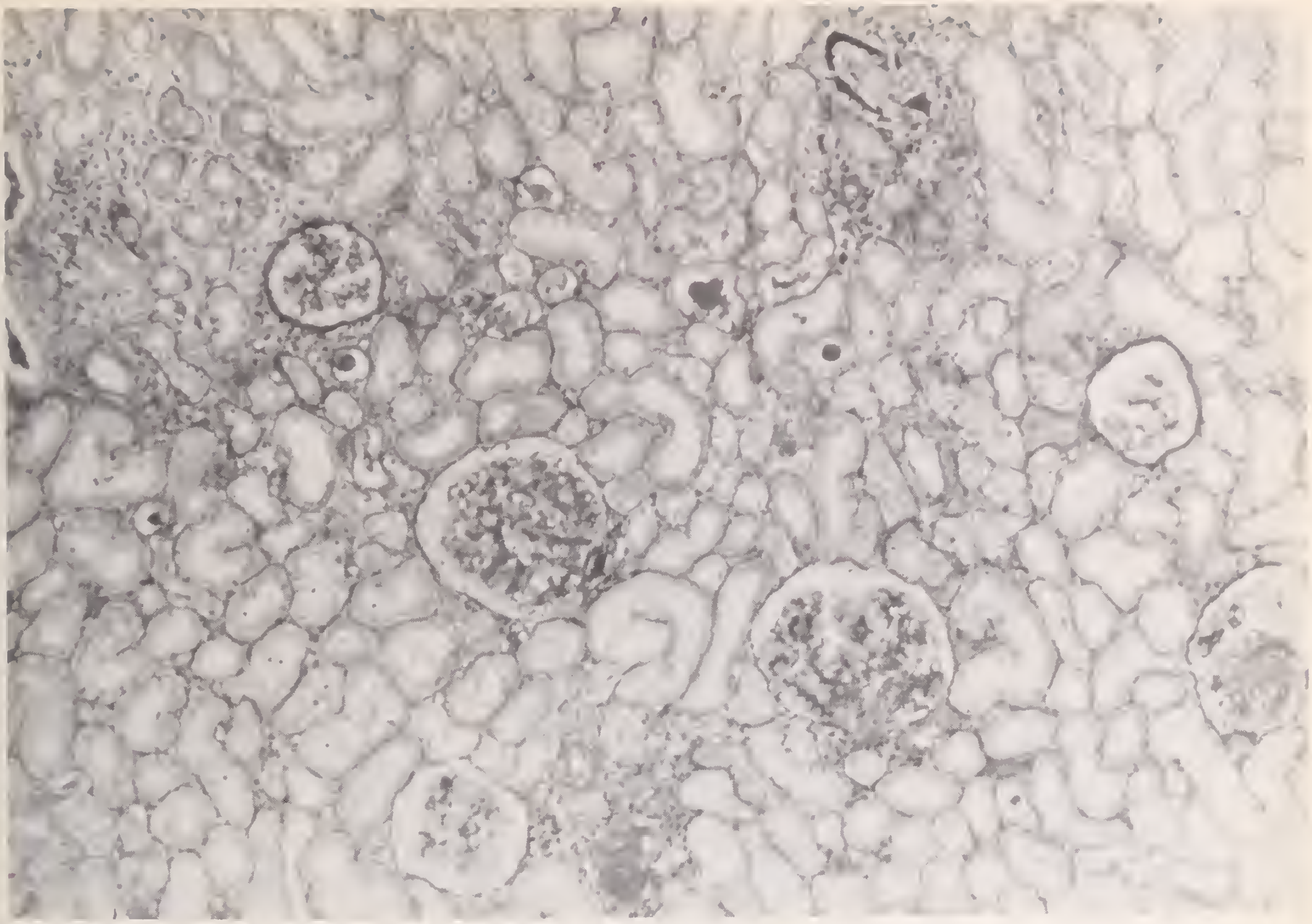

FIG. 3. Diffuse lupus glomerulonephritis in kidney with thickening of Bowman's capsule.

Urinary protein remained 2 gm/24 hrs. The hematocrit during the period stabilized although absent bowel sounds and blood tinged sputum remained. Multiple blood, urine, sputum, and endocervical cultures were negative; however, the low grade fever between 100–101 F° also persisted. Cyclophosphamide (100 mg QD) was added to the regimen.

Postoperative day 8: A second spinal tap was performed that revealed an opening pressure of 300 mm H20, a total protein of 200 mg/100 ml, and serosanguineous fluid. Spontaneous respirations ceased shortly after that, and the patient expired two days later on postoperative day 10.

Pathology

Postmortem examination revealed the cause of death to be hemorrhagic pneumonia secondary to diffuse lupus pneumonitis. Accompanying the hemorrhagic pneumonitis was hemorrhagic necrotizing laryngo-tracheo-bronchitis. Grossly, both lungs were enlarged, and each alveoli was consolidated with blood (Fig. 1). Granular immune complex deposits (IgG and fibinogen) were demonstrated on the capillary walls in the alveoli (Fig. 2). These deposits initiated an acute inflammatory response which led to diffuse alveolar injury and hemorrhage (Fig. 1). Because these complexes were granular, the disease process was associated with lupus erythematosus rather than with Goodpasture's syndrome. The possibility of viral or bacterial infection leading to the diffuse alveolar injury could not be completely ruled out; however, no organisms were cultured from the patient.

The kidneys were enlarged, and microscopic exam revealed diffuse lupus nephritis (Fig. 3). This was verified by the existence of thickened Bowmen's capsules (Fig. 3), wire loop lesions (Fig. 4), hematoxylin bodies, and thickened basement membranes in tubules. Immunofluorescence further demonstrated the presence of immune complexes in glomeruli and tubules (IgG, IgM, and fibrinogen).

In addition to the obvious involvement of the disease process in the lungs and kidneys, examination of other organ systems revealed generalized lymphadenopathy,

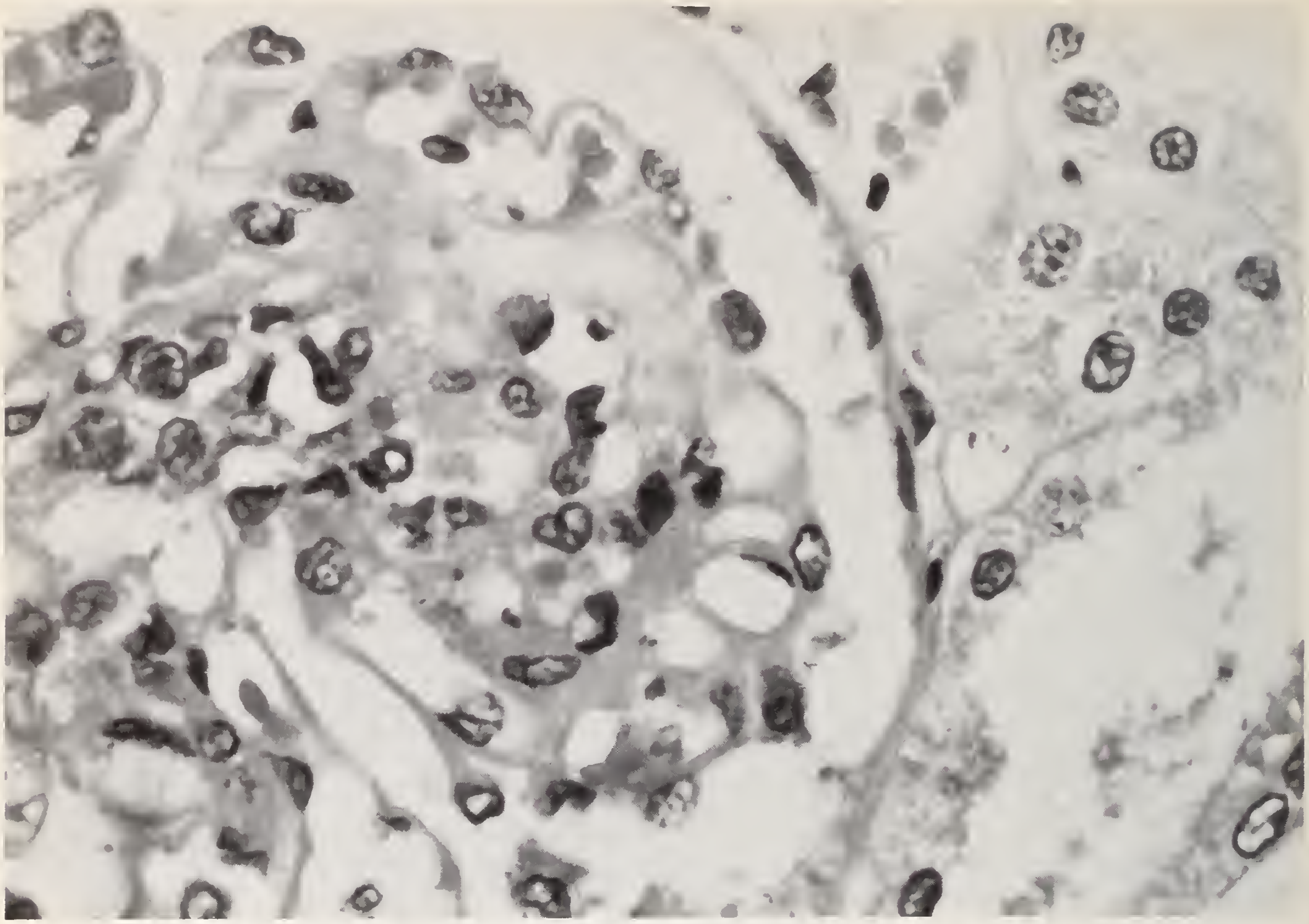

FIG. 4. Wire loop lesions in the glomerulus.

splenomegally, hepatomegally, and subarachnoid hemorrhages.

Discussion

The effect of pregnancy on systemic lupus erythematosus is unpredictable (5, 6, 10). Friedman's early observation that one third of the patients develop exacerbation during pregnancy, one third develop remission, and one third remain unchanged became widely accepted (2). Further reports, however, have shown that risk of exacerbation actually outweighs the prospects of remission by three to six times (4, 7). Once exacerbation develops during pregnancy it tends to remain throughout the pregnancy (5). The postpartum period is a particularly critical time, especially the first four weeks (3–5, 8, 11, 12). During this period, reports have shown exacerbations to be increased from three to eight fold (4, 8). The immediate postabortal period has been shown to be associated with the same risk (3, 4, 6, 12). If remission develops during pregnancy, however, it tends to remain as such throughout the pregnancy and the postpartum period (5).

Although an increased risk of exacerbation associated with pregnany and delivery has been demonstrated, no real permanent effect on the disease state has been shown as long as advanced cardiac and renal involvement is lacking. Renal involvement, in particular, has been shown to be associated with increased maternal mortality (3, 4, 7). A fifty percent increase in mortality has been demonstrated with lupus nephritis (4). Maternal mortality secondary to other manifestations of SLE such as lupus pneumonitis is very rare (7).

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Dysrhythmias and Enflurane Anesthesia

MARGARET G. PRATILA, M.D.*, VASILIOS PRATILAS, M.D., AND HARRY SMITH, Jr., Ph.D.**

Abstract

This study was designed to evaluate the effects of enflurane anesthesia, with or without administration of atropine 0.1 mg/10 kg, two minutes prior to induction of anesthesia on the incidence and severity of cardiac dysrhythmias during induction of anesthesia and endotracheal intubation. Dysrhythmias, except for mild slowing of the heart rate in the nonatropine group, were confined to the atropine group. Dysrhythmias consisted of atrial premature contractions and an occasional ventricular premature contraction.

Introduction

Enflurane produces a stable cardiovascular system with few dysrhythmias during normal clinical use (1, 2). Dysrhythmias described thus far have included premature ventricular contractions, bradycardia, absent P waves, premature atrial contractions and nodal rhythm. These have, however, occurred rarely and have been of short duration (3–7). This study was designed to evaluate the effect of enflurane, with or without prior use of atropine, on the incidence and severity of cardiac dysrhythmias during the induction of anesthesia and tracheal intubation.

Materials and Methods

Forty patients (A.S.A. physical status 1 or 2), ranging in age from 16 to 72 years old that were scheduled for surgery, were divided into two groups. Those with a history of cardiovascular problems were excluded. Although patients were chosen at random, we ensured that there were ten patients above 50 years of age and ten patients below 50 years of age, in each group. Group I patients were given atropine iv 0.1 mg/10 kg/2 minutes prior to induction of anesthesia. Group II patients received no atropine. No other premedication was given in either group.

Anesthesia was induced with sodium thiopental iv (average dose 3.5 mg/kg). After endotracheal intubation following succinyldicholine 80–100 mg iv, anesthesia was maintained with enflurane 1–1.5% in 50% nitrous oxide/oxygen at 6 L/minute flow in a semi-closed system (M.A.C. of Enflurane at 60% nitrous oxide = 0.93%) (8).

On arrival in the operating room area, patients were placed on the Electrodyne ST-219 telemetry monitor equipped with a direct write out. Each patient was monitored on Lead II and a basic tracing was taken. Continuous recording was started two minutes prior to induction and continued until after assisted respiration was started. The ECG was marked at that time into phases that would be evaluated later. These phases (Table I) were:

(1) an initial tracing
(2) post-atropine (in Group I)
(3) post-thiopental
(4) post-succinyldiocholine
(5) post-intubation
(6) enflurane during controlled ventilation
(7) enflurane during assisted ventilation.

No surgery was performed during the study period. Blood pressure and pulse were measured every minute during the time of investigation. PaO_2, $PaCO_2$, pH and hemoglobin saturation were measured after induction and again after intubation (Table III).

Results

The two groups showed no significant difference in preanesthetic heart rate (Table II). In the control group (Group II) no dysrhythmias were noted except for a mild slowing of the heart rate following the administration of succinyldicholine or intubation in 45% of patients. The change in rate, at each phase of the study, is shown in Figure 1 as the mean ±1 standard error of the mean. Heart rates rose following administration of Enflurane (Fig. 1).

In the atropine group (Group I) an occasional ventric-

From the Department of Anesthesiology, *Beth Israel Medical Center and Mount Sinai School of Medicine, CUNY, and the **Department of Biostatistics, Mount Sinai School of Medicine, New York, N.Y.

Requests for reprints should be sent to M. G. Pratila, M.D., 150 East 69 Street, New York, New York 10021.

TABLE I

Mean Observation Time in Minutes

	Mean	S.D.
Pre-anesthesia phase	2	0
Thiopental phase	1.1	0.2
Succinylcholine phase	1	0.2
Intubation phase	0.8	0.3
Enflurane (controlled ventilation)	3.2	0.2
Enflurane (assisted ventilation)	4.4	0.5
Mean observation time/patient	12.4	0.3

TABLE II

Average Heart Rate during Pre-anesthetic Phase

Group	Mean	STD. DEV.	S.E.M.
Atropine	77.05	13.68	3.06
Non-atropine	82.55	17.99	4.02
t = 1.09 N.S.			

TABLE III

Mean Values of paO_2, $paCO_2$ and pH two minutes before intubation and two minutes after intubation

		paO_2 (mm Hg)	$paCO_2$ (mm Hg)	pH
Before intubation (FiO2 = 1)	ȳ	441.55	36.9	7.41
	s	38.23	3.14	0.02
After intubation (FiO2 = 0.5)	ȳ	209.4	38.45	7.40
	s	14.79	2.09	0.02

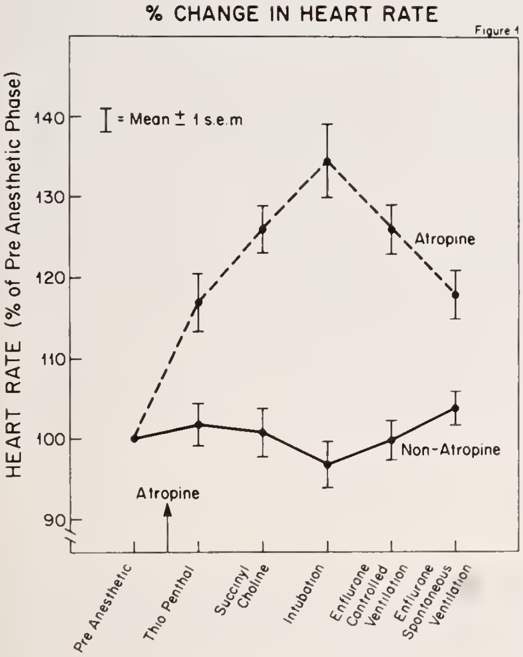

FIG. 1. The change of heart rate expressed as a percentage of the reanesthetic phase shows a marked rise in the atropine group to a aximun at the time of intubation. Following enflurane administration, ere is a rapid fall in rate. The nonatropine group shows a moderate ll in rate which is maximal at the time of intubation. Following flurane administration there is a rise in rate.

ular premature contraction (VPC) was noted following intubation in two patients, which was associated with more frequent atrial premature contractions in one (Fig. 2). These cleared when enflurane anesthesia was instituted. Another patient developed an occasional VPC with a retrograde P wave following the administration of atropine iv (Fig. 3). This dysrhythmia cleared following the administration of sodium thiopental. There was a rise in pulse rate following the administration of atropine that reached its maximum following intubation. The increase in heart rate at this phase of the study is shown in Figure 1. Following endotracheal intubation, heart rates fell with a further fall following enflurane administration (Fig. 1).

Although mean blood pressure (diastolic pressure + ⅓ pulse amplitude) decreased by 23 ± 2.8 mm Hg during maintenance of anesthesia, there was no consistent correlation between blood pressure, heart rate and dysrhythmic episodes. There was no significant difference in blood pressure between the atropine and nonatropine groups at different phases of the study. Blood pressure was highest during the phase of endotracheal intubation.

Discussion

A significantly higher incidence of dysrhythmias has been shown in patients given atropine prior to induction of anesthesia when halothane was used for maintenance of anesthesia than in patients not given atropine (9). Atropine is known to block the parasympathetic nervous system of the heart resulting in an unopposed accelaration effect from its sympathetic innervation (10). After tachycardia, simple A-V dissociation is the most common cardiac effect reported (11). Nodal (junctional) premature contractions and ventricular premature contractions have also been described (12). Massumi and his coworkers have described ventricular tachycardia and fibrillation following intravenous atropine for the treatment of bradycardias (13). Morton and Thomas have suggested that initially atropine stimulates vagal activity centrally and blocks it peripherally (14). Averill and Lamb (11) suggested that atropine has three distinctive effects on the heart. First a vagotonic effect, followed by a transient period of vagal imbalance at different levels of the conducting system and, finally, a prolonged period of parasympathetic blockade. A-V dissociation occurs rapidly which indicates it occurs during the brief vagotonic phase while ventricular bigeminy appears later when vagal blockade is established (15). Other investigators (12) have described a greater incidence of dysrhythmias but this varied with anesthetic agents. Patients receiving halothane had a 40% incidence of dysrhythmias while those anesthetized with thiopental/N_2O did not develop

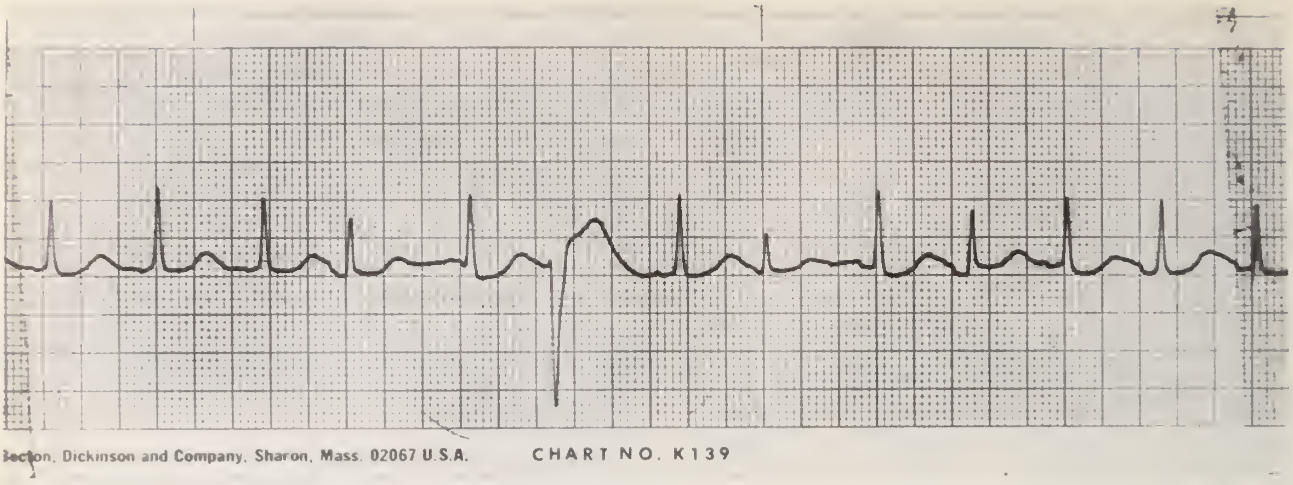

FIG. 2. Atrial premature contractions with an occasional ventricular premature contraction in a patient who had received Atropine following endotracheal intubation.

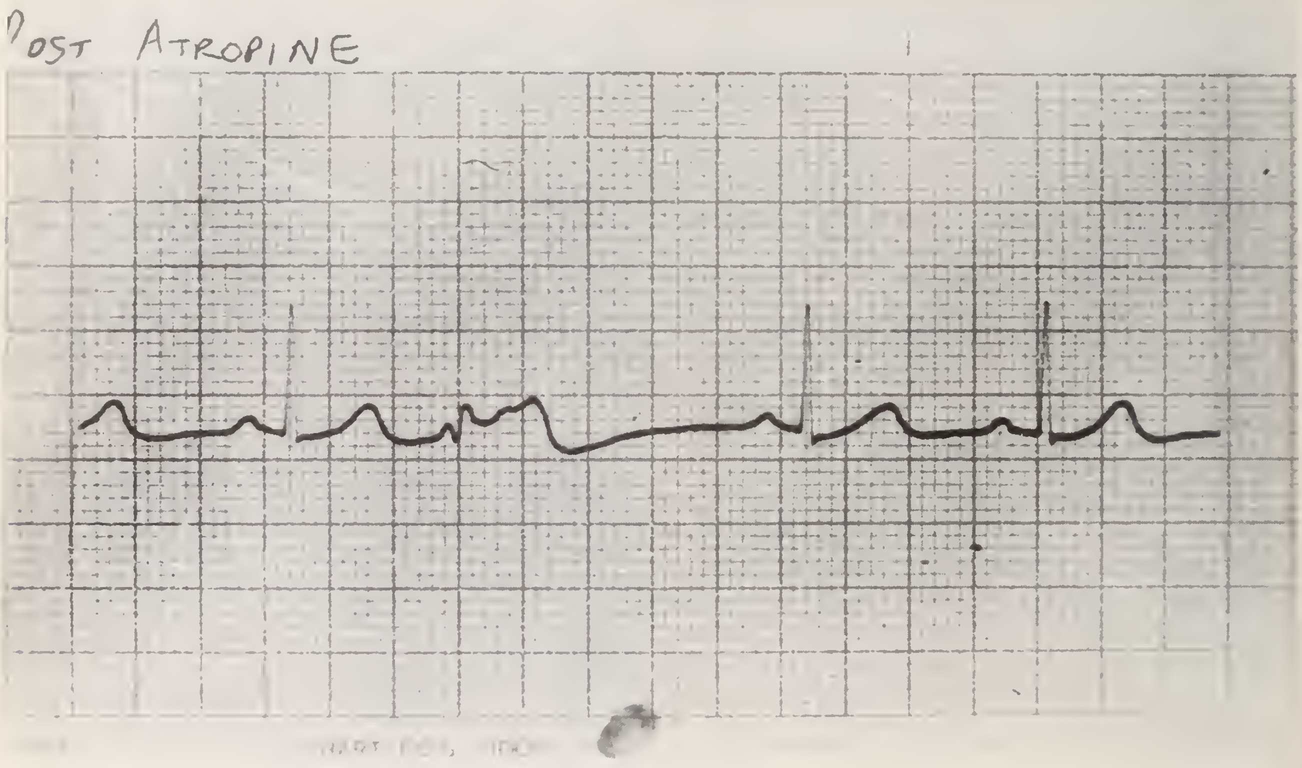

FIG. 3. An occasional ventricular premature contraction with a retrograde P wave following the administration of Atropine.

dysrhythmis. With cycloproprane, there was a 77% incidence of dysrhythmia, the majority being ventricular in origin. With larger doses of atropine 3 mg iv, compared to 0.4 mg iv, the incidence of dysrhythmias was less, possibly caused by obviation of the early vagotonic phase (15). Heart rate increases under various anesthetic agents were statistically significant only between cyclopropane and halothane and enflurane. There has been adequate work done to explain the mechanisms whereby halothan produces dysrhythmias. Although halothane has anti dysrhythmic properties, as evidenced by its effect o phase 4 depolarization of the cardiac action potentia (16), it has dysrhythmic properties particularly in th presence of epinephrine. These are believed by Zink an Hashimoto to be re-entry phenomena (17, 18).

Far less is known regarding enflurane. Krishna an

Paradise (19) have shown in isolated rat atria that enflurane has a dose-dependent positive chronotropic effect which is, however, of lesser extent than that produced by methoxyflurane or diethyl ether. Atlee and his coworkers have shown that enflurane (20) and halothane (21–23) prolong atrioventricular nodal conducting time in both spontaneously beating hearts and during incremental increases in atrial paced rates. Unlike halothane, enflurane does not prolong His-Purkinje or ventricular conduction time. If re-entry of impulses is an important mechanism in the production of dysrhythmias during halothane anesthesia, this may explain why ventricular dysrhythmias are less common during enflurane anesthesia. Enflurane, despite similarities in chemical structure, does not appear to have the same effect on the ventricular conducting system as methoxyflurane. With methoxyflurane the combination of primary pacemaker depression and secondary pacemaker stimulation favors shift of pacemaker activity to the ventricular conducting system (24, 25).

There is sufficient evidence to suggest that enflurane has less dysrhythmic effects in the presence of epinephrine compared to other halogenated anesthetic agents. This has been shown in both animals (26–28) and clinical studies (29, 30). The many reports of lack of dysrhythmias during enflurane anesthesia for pheochromocytoma (31–34) also attest to its ability to maintain stable cardiac rhythm despite raised catecholamine levels. The lack of dysrhythmias in our control group and the rapid disappearance of dysrhythmias produced by atropine and endotracheal intubation are further evidence of the stable cardiovascular state during enflurane anesthesia.

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Pilomatrixoma: An Unusual Presentation

ELLEN BLANK, M.D., T. JOTHIKUMAR, M.D., JACK ALBERT, M.D., AND LEONARD KORNBLEE, M.D.

Introduction

Pilomatrixoma, or calcifying epithelioma of Malherbe, is a relatively uncommon appendageal tumor, believed to originate from hair matrix cells. It usually appears spontaneously as an asymptomatic, solitary nodule either on the face, arms or upper trunk. We report the unusual case of this lesion as a tender, posttraumatic, violaceous nodule occurring on the lower extremity, simulating an organized hematoma.

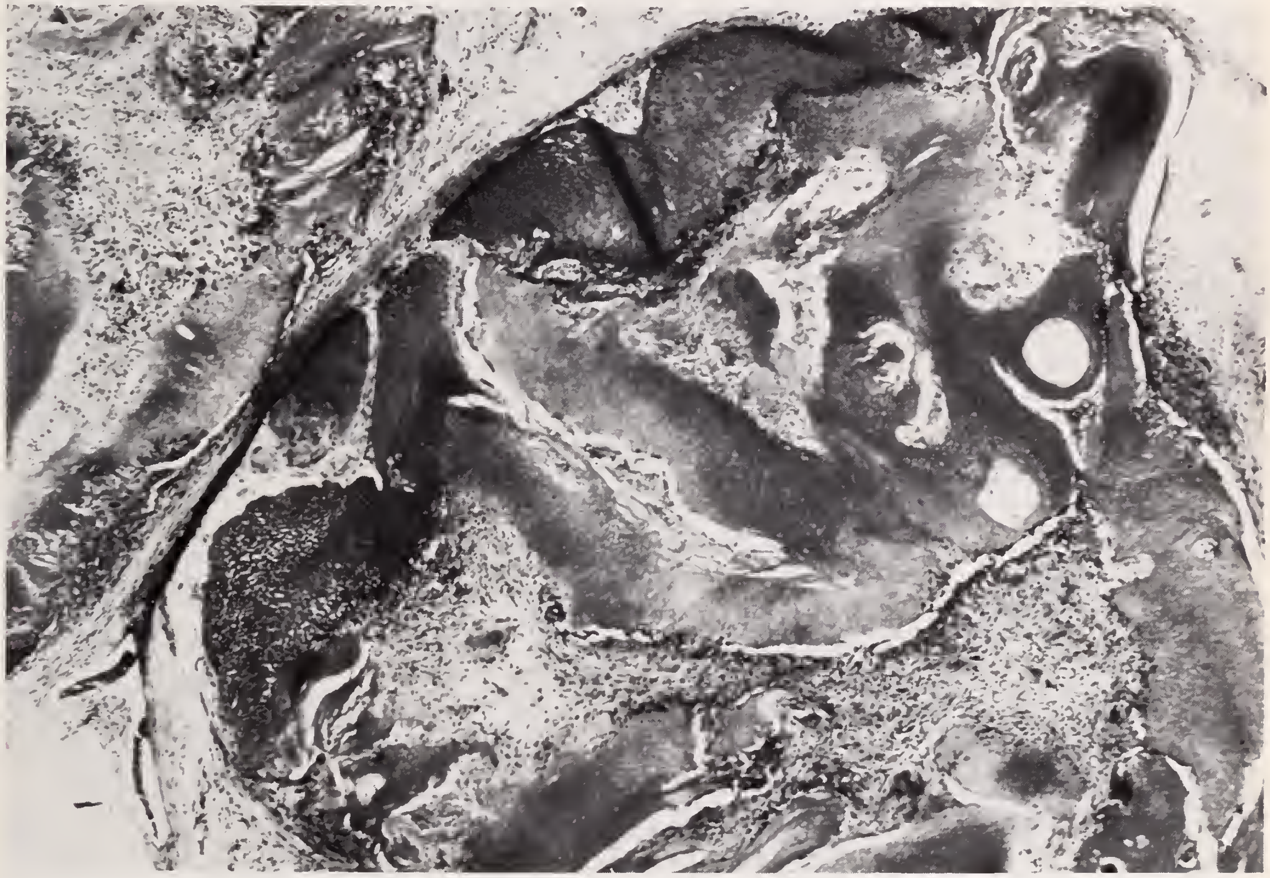

FIG. 1. Encapsulated dermal nodule showing cellular islands with surrounding connective tissue stroma (Hematoxylin and eosin, original magnification × 20).

Case Report

A twenty-three-year-old Puerto Rican male had a tender mass on the right posterior calf. He related the onset of the lesion to an episode of blunt trauma three months prior to examination, and noted progressive enlargement during this period. The medical history was otherwise unremarkable.

From the Departments of Dermatology and Pathology, Bronx Veterans Administration Hospital, and the Department of Dermatology, Mount Sinai School of Medicine of The City University of New York.

Reprint requests should be sent to Dr. Blank, Department of Dermatology, The Mount Sinai Hospital, One Gustave L. Levy Place, New York, NY 10029.

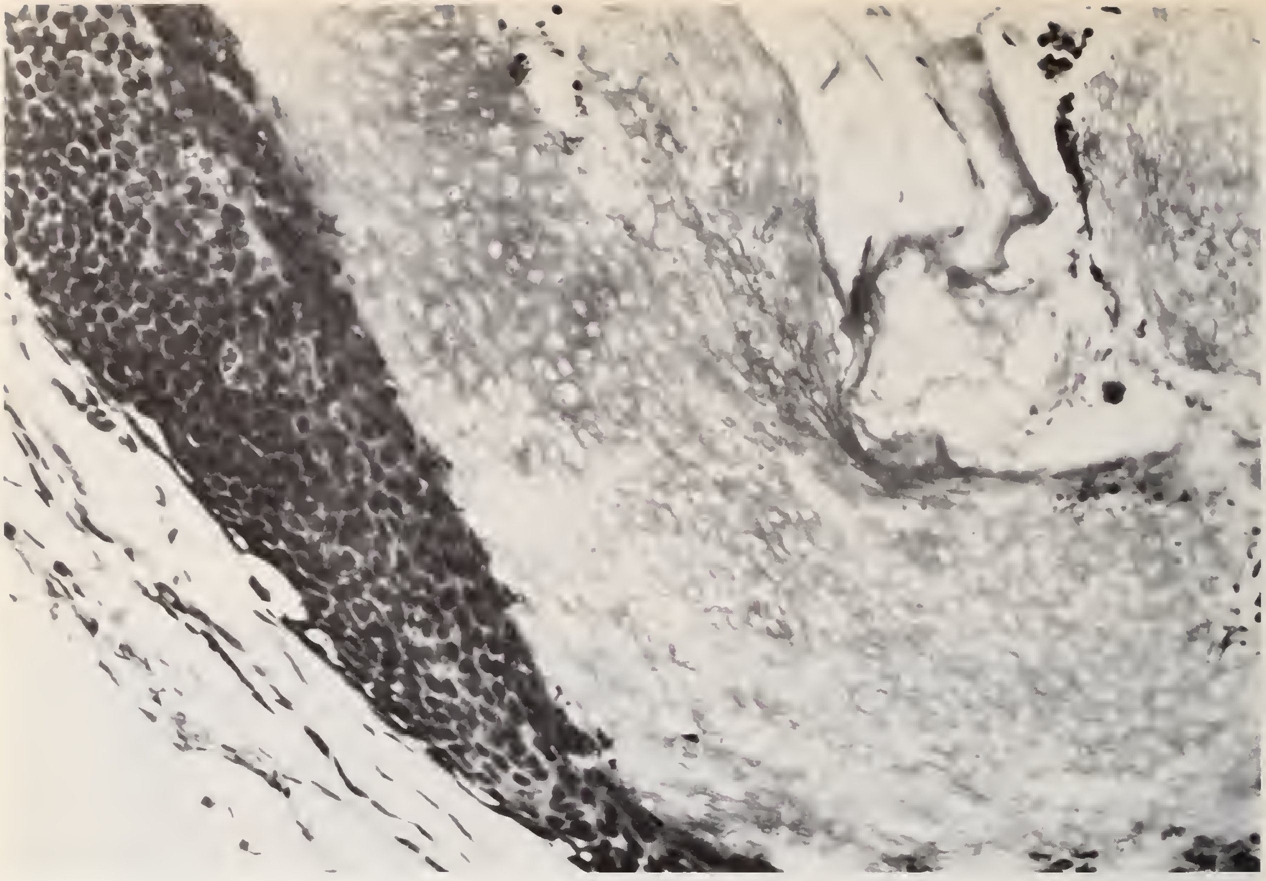

FIG. 2. Tumor island with peripheral, densely packed basophilic cells and central, pale-straining shadow cells (Hematoxylin and eosin, original magnification × 100).

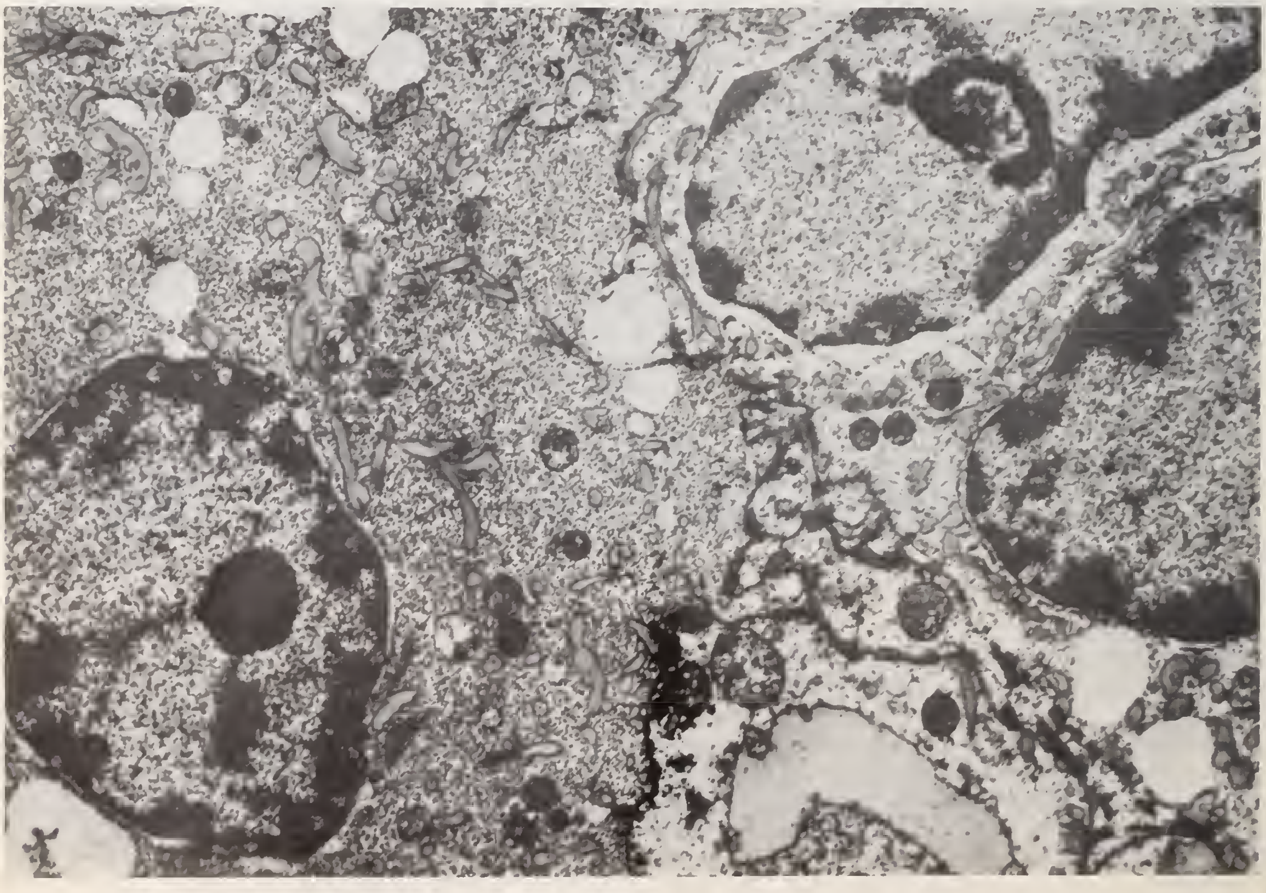

FIG. 3. Basophilic cells with oval nuclei, tonofilaments and occasional desmosomes (Electron microscopy, original magnification × 28,000) Note: Formalin artifacts in all sections.

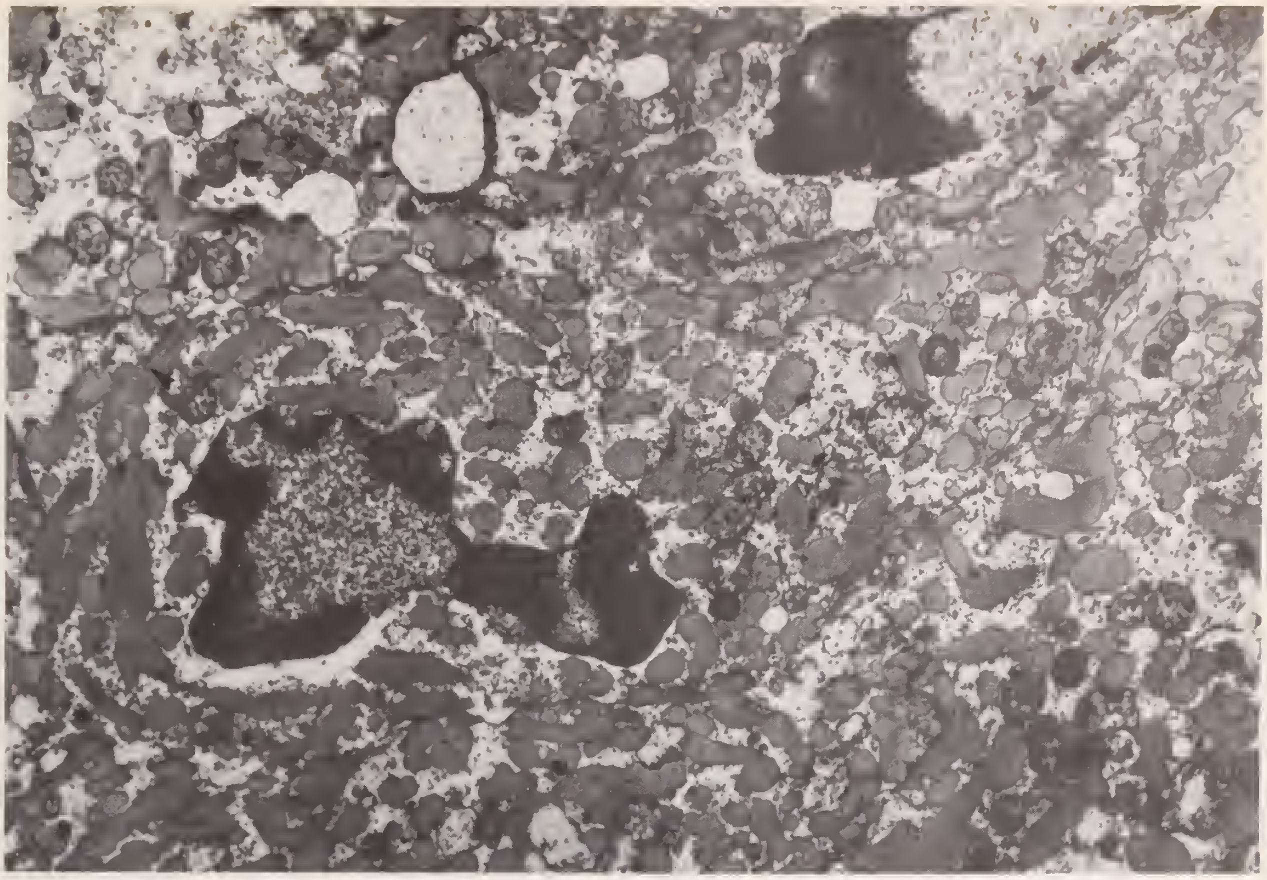

FIG. 4. Transitional cells with prominent parallel tonofilaments (Arrow). (Electron microscopy, original magnification × 28,000).

On inspection, a 2.5 × 3.5 cm. violaceous mass was visible over the right posterior calf. The overlying epidermis was smooth and had a bruised appearance with varying shades of violet, blue and brown. Palpation revealed a tender, freely movable nodule. The lesion did not transilluminate. No other skin abnormalities were noted.

The clinical impression was that the lesion was an organized hematoma, and the lesion was excised without complications.

Histology

The specimen consisted of an encapsulated, grayish yellow, 7 cm globular mass. Histologically, irregular islands of basaloid squamous epithelium were seen, with surrounding connective tissue, characteristic of pilomatrixoma (Figs. 1, 2). Foreign body giant cells and small foci of calcification were also noted. Electron microscopic analysis further defined the lesion. The basophilic cells were noted to contain oval nuclei, tonofilaments and occasional desmosomes (Fig. 3). The transitional cells contained layers of tonofilaments in parallel arrangement around the nucleus, but without keratohyaline granules (Fig. 4). The shadow cells showed few tonofilaments and a faded nuclear outline (Fig. 5) (1).

Discussion

Pilomatrixoma was first described by Malherbe and Chenantais in 1880 as a calcifying epithelioma of sebaceous glands (2). The true incidence of this lesion is unknown; however, of 140,000 dermatohistopathologic specimens examined at one institution, 170 cases of pilomatrixoma were found (1:824 specimens) (3). Topographically, the lesion is noted in decreasing order of frequency on the head, upper extremity, neck, trunk and lower extremity (4), with only 5% of lesions occurring below the waist (5). Clinical characteristics of the lesion vary. It usually appears spontaneously as an asymptomatic solitary nodule covered by normal skin (6). Less common features include pain on palpation, a history of antecedent trauma, and a reddish blue discoloration overlying the lesion (5).

Histopathologically, this lesion consists of cellular islands of basophilic and shadow cells contained in a connective tissue stroma. Foreign body giant cells are noted

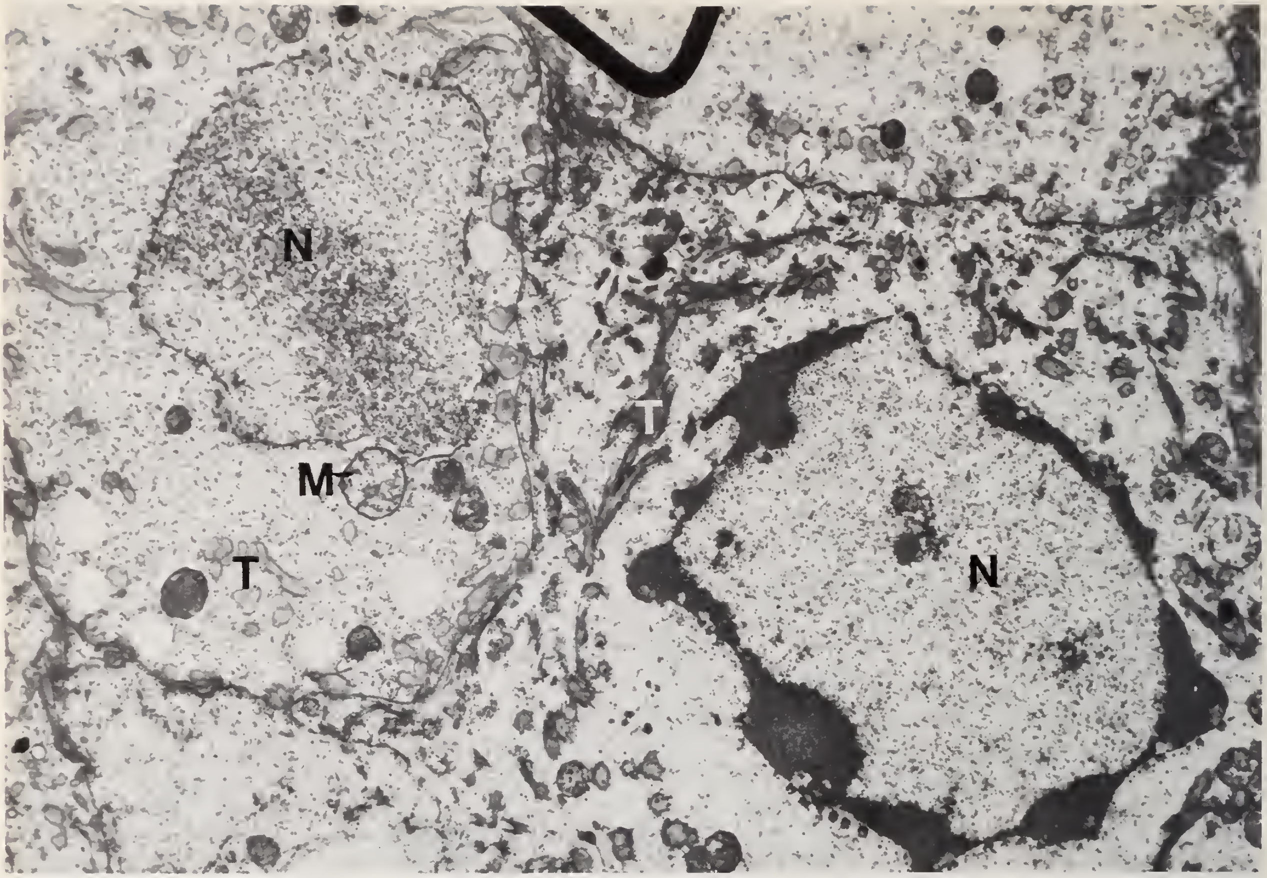

FIG. 5. Shadow cells with few tonofilaments (T) and degenerating nucleus (N), Mitochondria (M). (Electron microscopy, original magnification × 28,000).

frequently within the stroma. Calcification occurs in approximately 75% of cases, is usually present within the central shadow cells, and may also be seen in the stroma. The central shadow cells are eosinophilic, pale-staining cells, that appear to be nonnucleated on light microscopy. Electron microscopy reveals these cells to contain a faded nucleus surrounded by concentric keratin fibrils. Basophilic cells that make up the periphery of the cellular islands contain both desmosomes and tonofilaments. The "transition" cell, which lies between the basophilic and shadow cell, contains parallel tonofilaments without keratohyaline granules. The process of keratinization without the formation of keratohyaline granules lends support to the theory that pilomatrixoma arises not from sebaceous glands, as originally described, but from immature hair matrix cells.

Pilomatrixoma is an uncommon clinical entity, usually arising spontaneously as an asymptomatic solitary nodule on the face, arms, or upper trunk. We report the unusual presentation of this lesion as a tender, posttraumatic, violaceous nodule occuring on the lower extremity, simulating an organized hematoma.

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Hyperkalemia in Chronic Stable Renal Disease

THOMAS KAHN, M.D.*, D. M. KAJI, M.D.*, GIORGIO NICOLIS, M.D., Ph.D.**, LAWRENCE R. KRAKOFF, M.D.,***
and RICHARD M. STEIN, M.D.*

Abstract

Plasma aldosterone, plasma renin activity (PRA), and electrolyte excretion were compared in 12 consecutive patients with persistent hyperkalemia and chronic renal disease and nine normokalemic azotemic patients. Plasma aldosterone and PRA were normal in seven hyperkalemic patients, suggesting that hyperkalemia in azotemic subjects often is not consequent to the low renin, low aldosterone syndrome.

Introduction

Several investigators have identified a group of subjects with chronic stable renal disease who have persistent hyperkalemia, low plasma renin activity (PRA), and low plasma aldosterone (1–3). It has been suggested that, in these subjects, low renin production results in low plasma aldosterone and consequent hyperkalemia (1–3). To evaluate if this constellation of findings is the usual explanation for hyperkalemia in subjects with chronic stable renal disease, we studied 12 consecutive patients with persistent hyperkalemia and compared the results to those obtained in nine subjects with renal disease who had normal plasma potassium.

Materials and Methods

All patients were asymptomatic with stable weight and blood pressure, and had no evidence of edema, congestive heart failure, or cirrhosis. They were not receiving any medications known to influence potassium, PRA, or aldosterone. None of the patients required dialysis, and average daily urine output ranged from 825 to 2100 ml. Daily 24-hour urines were analyzed for sodium, potassium, and creatinine. Blood samples for aldosterone, PRA, and plasma potassium were obtained at noon preprandially after the subjects were ambulant. Plasma renin activity and plasma aldosterone were measured by radioimmunoassay (4, 5). Informed consent was obtained from all subjects and the protocol was approved by the hospital research committee.

Group I consisted of 12 patients with chronic stable renal disease and persistent hyperkalemia (plasma potassium > 5.6 mEq/1). Group II consisted of nine patients with chronic stable renal disease with normal plasma potassium. All subjects were maintained for a period of 10–30 days on a diet containing 83 mEq sodium and 50 mEq potassium.

Results

Pertinent data from each patient are listed in Table I. The values for plasma aldosterone, PRA, potassium, and bicarbonate represent the average of two to five specimens. Urine electrolyte values represent the average of the daily collections from the entire period of study. Plasma aldosterone levels in normal subjects upright on an ad libitum diet are 7-22 ng/100 ml and PRA values 1.5-5ng/ml/hr in our laboratory.

In four hyperkalemic patients, plasma aldosterone values were slightly lower than values obtained in the normokalemic group. In these patients, PRA values were also low, although not below values obtained in the normokalemic patients. Plasma aldosterone values in the other seven hyperkalemic patients were similar or even higher than values obtained in the normokalemic group, and PRA levels were normal or high in these patients.

Potassium excretion was similar in both groups. Mean daily sodium excretion was similar in the hyperkalemic and normokalemic subject (Table I), and all patients maintained a stable weight and blood pressure during the study. Plasma bicarbonate was modestly but significantly lower in the hyperkalemic subjects. Four of the hyperkalemic and two of the normokalemic patients had

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From the *Renal, and **Endocrine Divisions, Department of Medicine, Bronx Veterans Administration Medical Center, Bronx, N.Y. and ***Hypertensive Division, Department of Medicine, the Mount Sinai Hospital, N.Y.

Requests for reprints should be sent to Dr. Thomas Kahn, Veterans Administration Hospital, 130 West Kingsbridge Road, Rm. D-240, Bronx, N.Y. 10468.

TABLE I

Data are Presented from Individual Hyperkalemic and Normokalemic Patients. Plasma Renin Activity (PRA) in Nanograms of Angiotensin I Generated Per ml of Plasma Per Hour. P Values Were Determined Utilizing the Student t test for Unpaired Groups.

	Plasma K mEq/l	U_KV mEq/24 hrs	$U_{Na}V$ mEq 24 hrs	PRA ng/ml/hr	Aldosterone ng/100 ml	HCO_3 mEq/l	Creatinine Clearance ml/min	Diagnosis
GROUP I: *Hyperkalemia, Chronic Renal Disease*								
1) L.B.	5.7	34	27	5.2	19.6	25	40	glomerular sclerosis
2) M.B.	5.9	44	81	7.6	12.6	19	38	glomerulonephritis
3) J.F.	6.4	37	77	0.7	11.6	23	27	diabetes
4) S.P.	6.3	27	105	7.4	12.4	23	19	diabetes
5) R.A.	6.7	31	57	14.0	—	19	19	nephrosclerosis
6) H.I.	6.2	56	44	4.4	27.8	24	14	diabetes
7) W.S.	5.9	56	124	3.4	17.0	18	10	diabetes
8) S.S.	5.8	44	81	10.6	20.1	20	10	nephrosclerosis
9) J.W.*	6.0	—	—	12.2	13.8	17	8	chronic obstruction
10) I.S.	5.8	11	68	0.9	7.0	26	7	nephrosclerosis
11) H.H.	6.2	22	86	0.5	8.6	21	6	nephrosclerosis
12) J.H.	6.0	24	79	0.5	11.7	20	4	chronic obstruction
Mean ± S.D.	6.1 ± 0.3	35 ± 14	75 ± 27	5.6 ± 4.8	14.7 ± 6.0	21 ± 3	17 ± 12	
Group II: *Normokalemia, Chronic Renal Disease*								
1) G.A.	4.2	35	53	0.8	12.6	27	50	chronic obstruction
2) H.W.	4.5	42	53	4.6	—	29	45	diabetes
3) G.P.	4.8	25	53	2.5	16.0	22	35	glomerulonephritis
4) P.W.	4.9	55	47	4.2	17.2	27	28	nephrosclerosis
5) L.S.	5.0	20	20	2.3	15.3	21	19	gout nephropathy
6) C.K.	4.6	54	151	0.4	15.4	23	14	myeloma
7) B.S.	5.1	62	93	6.9	13.7	26	11	diabetes
8) J.L.	4.4	25	39	0.8	16.7	24	10	nephrosclerosis
9) T.V.	4.2	23	32	3.0	12.6	23	6	pyelonephritis
Mean ± S.D.	4.6 ± 0.3	38 ± 16	60 ± 40	2.8 ± 2.1	14.9 ± 1.8	25 ± 3	24 ± 16	
P Value	.001	NS	NS	NS	NS	.05	NS	

* Creatinine clearance obtained from recent previous collections.

diabetes mellitus but plasma glucose remained below 200 mg/100 ml during the study.

Discussion

Several investigators have identified patients with chronic renal disease and persistent hyperkalemia who have low PRA and plasma aldosterone value (1–3). In some of these patients hyperkalemia was corrected with replacement doses of fludrocortisone (0.1 mg/day) (1, 3); whereas, other patients apparently required considerably larger doses (2, 6). Persistent hyperkalemia has, however, been reported in a few patients despite normal levels of plasma aldosterone (7–9).

In four of our hyperkalemic patients, plasma aldosterone values were lower than those obtained in our control group (Table I). These patients also had low levels of plasma renin activity, although not lower than values observed in three of the normokalemic patients who had normal levels of plasma aldosterone. It is possible that these four hyperkalemic patients are similar to the hypoaldosteronemic patients reported by other workers (1–3), but the lack of correlation between levels of PRA and plasma aldosterone in either group suggests the low plasma aldosterone values in these four patients cannot be attributed primarily to low levels of PRA.

Seven out of 11 hyperkalemic patients had plasma aldosterone values that were indistinguishable from levels found in our control group (Table I). In other studies, we have demonstrated that plasma aldosterone values in normokalemic patients with chronic stable renal disease are comparable to values obtained in normal subjects [10]. PRA values in the hyperkalemic patients with normal aldosterone were similar or higher than those obained in our controls (Table I). Plasma bicarbonate was above 20 mEq/l in eight of the 12 hyperkalemic patients and hyperkalemia persisted with normal plasma bicarbonate in the patients with lowest plasma bicarbonate during this study. It seems unlikely, therefore, that the modest reduction in plasma bicarbonate in some patients is the sole explanation for the hyperkalemia. Four of our hyperkalemic subjects had diabetes mellitus but there was no relationship between plasma potassium and glucose levels. Although the ability of our hyperkalemic subjects to increase plasma aldosterone and PRA under conditions of stress was not evaluated, the present studies suggest that a number of patients with chronic renal disease maintain persistent hyperkalemia under basal conditions despite normal levels of plasma aldosterone and PRA. The levels of plasma aldosterone in the hyperkalemic patients may be lower than is appropriate for the level of plasma potassium, possibly suggesting some alteration in the ability of potassium to stimulate aldosterone in these patients. However, the levels of aldosterone are generally within the range seen in normokalemic patients with chronic renal disease given an additional 50 mEq of KCl added to the diet (10). Moreover, there does not appear to be a correlation of the plasma aldosterone values with the levels of PRA (Table I), indicating that a defect in renin production is not the primary problem (1, 2).

The finding that potassium excretion in the hyperkalemic patients was similar to that in the normokalemic patients suggests that the ability to excrete potassium is maintained, albeit at a higher plasma concentration, and helps to explain why plasma potassium does not rise progressively in the hyperkalemic patients. Potassium excretion depends primarily on potassium moving down a concentration gradient from renal tubular cell to tubular lumen (11). It is possible that in the hyperkalemic subjects adequate renal tubular cell concentration and adequate potassium excretion can only be achieved as a consequence of a high plasma potassium. A defect in membrane transport has been described in azotemic subjects (12–14), and it is possible that the hyperkalemia in our patients is consequent to an exaggeration of such an alteration in potasium transport into cells (10).

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Spontaneous Migration of an Intracranial Bullet Fragment

SHELDON M. WASSERMAN, MD AND JEFFREY A. COHEN, MD

Abstract

The civilian experience with nonsurgical management of gunshot wounds to the head with a remaining intracranial foreign body (bullet) has been limited. In this case report, the spontaneous movement of a bullet within the cerebellum is documented by radiographs and computerized axial tomography. During a nine-day period, the bullet migrated from a position near the fourth ventricle to its point of entry in the occipital bone, a site of ready surgical accessibility. The physical factors playing a role in such migrations are discussed.

Introduction

Since the initial use of radiographic techniques to investigate penetrating cranial missile injuries, many reports have described the spontaneous movement of intracerebral metallic fragments (1–6). The bulk of the literature suggests that such moving fragments are relatively uncommon and that they are indicative of severe complications of the original injury.

As with most data on cerebral missile injuries, the information on migration of metallic fragments is derived largely from wartime series. It is now apparent that civilian missile injuries differ in many respects from wartime injuries (7). Recently, we treated a patient who sustained a gunshot wound to the brain in civilian life. His benign course was associated with the movement of the bullet from a deep intracerebral location to a peripheral, surgically accessible site.

Case Report

The patient was a 21-year-old right-handed taxi driver, previously in excellent health, who sustained a gunshot wound to the head during a robbery on July 2, 1978. The weapon involved was a small caliber hand gun. The patient was taken immediately to a local hospital and on the following day was transferred to The Mount Sinai Medical Center. Examination at that time revealed that the patient was slightly lethargic but fully oriented and able to recount the events of the previous night. Vital signs were normal. There was a two centimeter entrance wound with blackish discoloration at the lower left occiput. The remainder of the general physical examination was unremarkable. Pupillary responses, fundiscopic examination and visual fields were normal. Extraocular

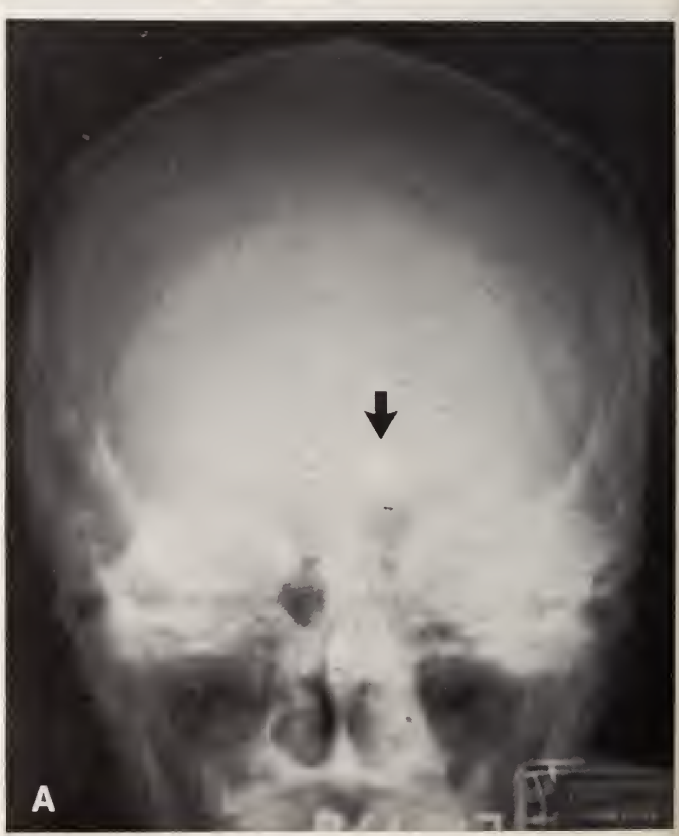


FIG. 1A

From the Department of Neurology, Mount Sinai School of Medicine (CUNY) and The Mount Sinai Hospital, New York, NY.

Requests for reprints should be sent to Dr. Sheldon Wasserman, Department of Neurology, Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, NY 10029.

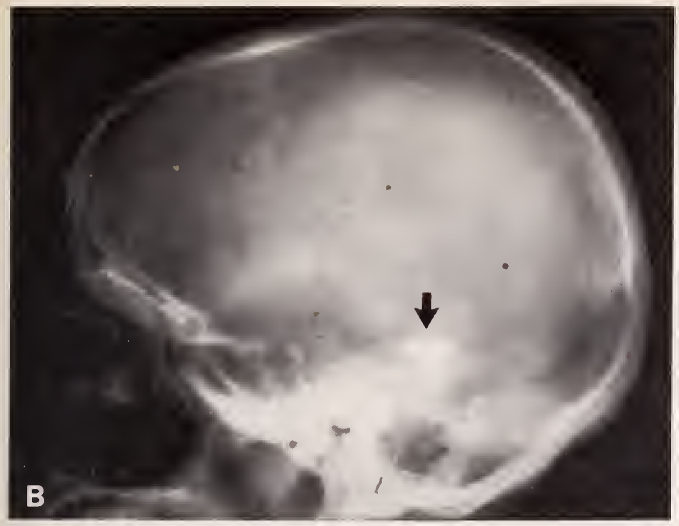
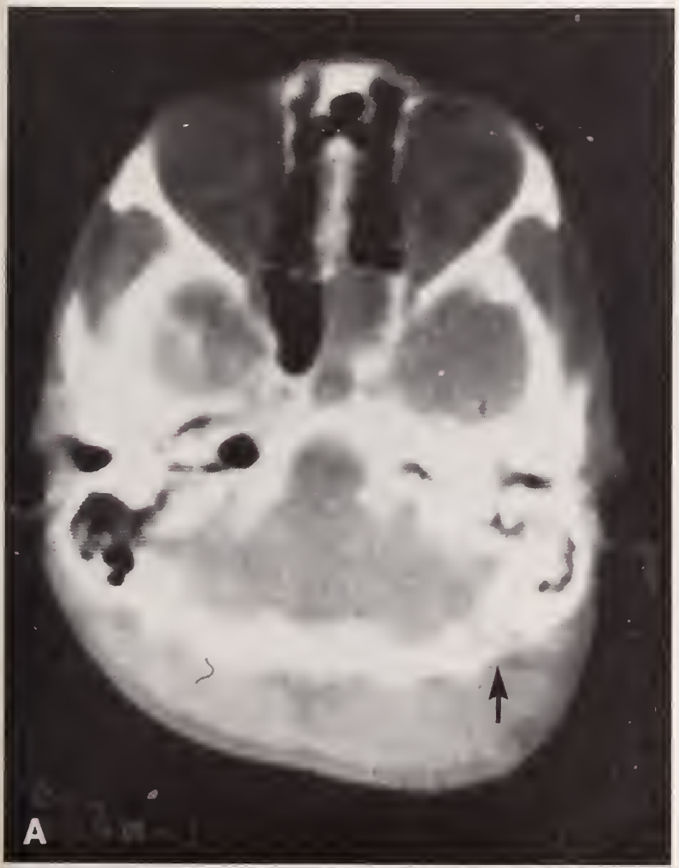
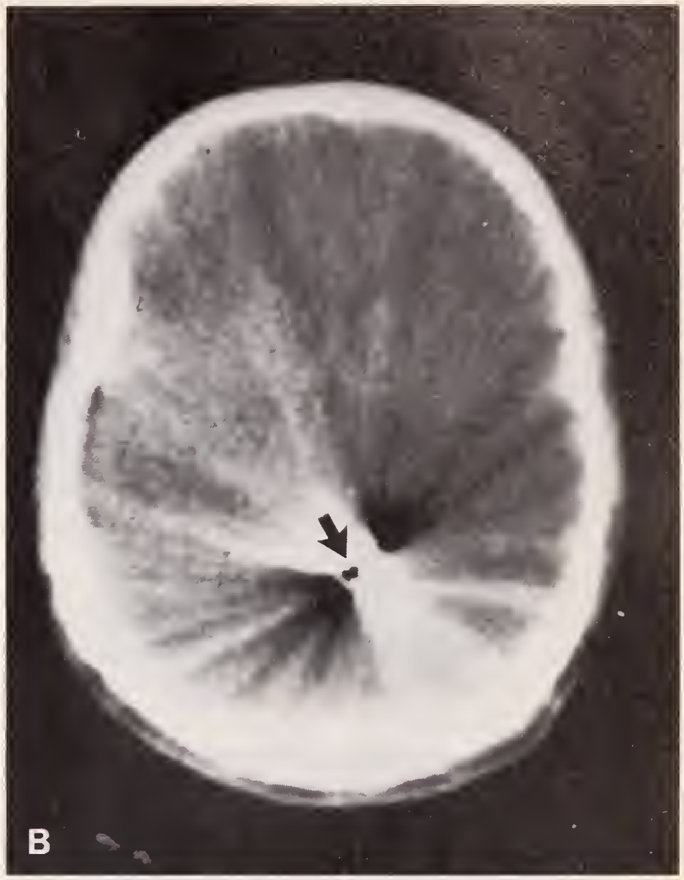


FIG. 1. Skull radiographs one day following injury. Bullet is located in superior left cerebellum near roof of fourth ventricle. Entrance wound is in left side of occipital bone near foramen magnum. Intracranial bone fragments are seen along bullet's path.





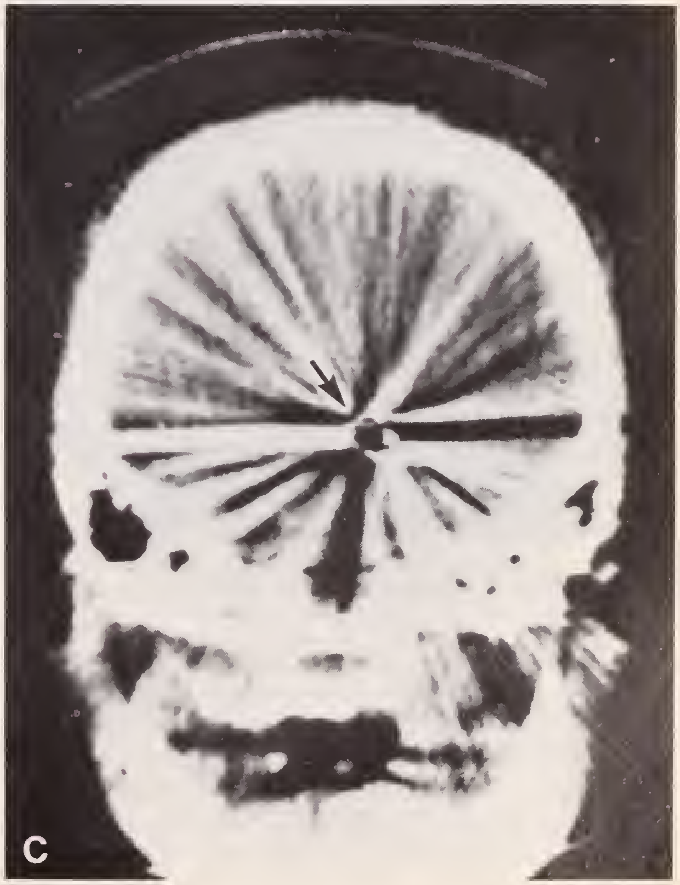


FIG. 2. CAT scan one day following injury. (A) View through posterior fossa shows superficial soft tissue swelling and entrance wound in occipital bone. (B) Upper edge of bullet is seen in scan cut through frontal horns. (C) Coronal section shows bullet's position in relation to petrous bones.

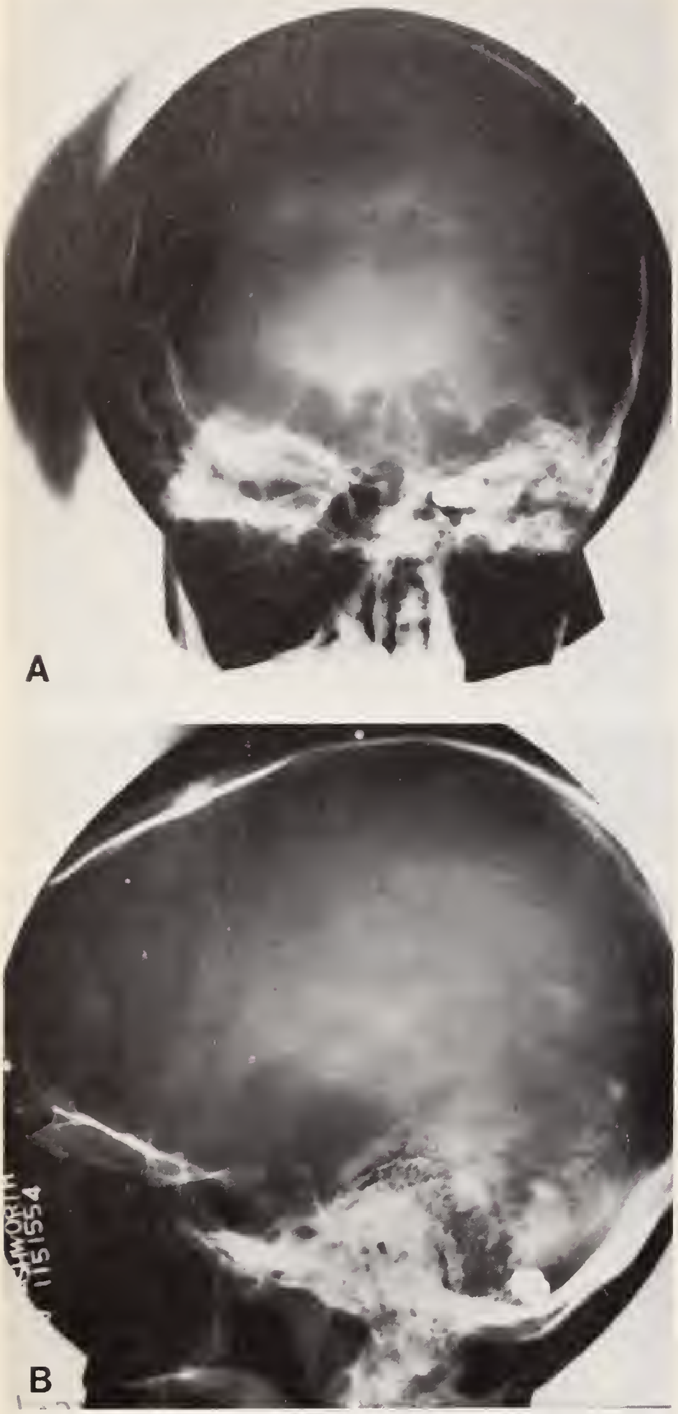


FIG. 3. Skull radiographs ten days following injury. Bullet has migrated to a site near the inner table of occipital bone.

movements were intact. There was horizontal nystagmus on lateral gaze and vertical nystagmus on upward gaze; the fast component was always in the direction of gaze. The nystagmus was of greatest amplitude on left lateral gaze, and the patient complained of diplopia when looking in that direction. Optokinetic responses were defective when the target moved from the patient's right to his left. Cold water caloric testing was normal. Ataxia and dysdiadochokinesis of the left extremities were present. When attempting to sit upright, he experienced severe vertigo and leaned toward the left. There were no other abnormalities on neurologic examination.

Skull radiographs revealed that the bullet was located in the posterior fossa, presumably in the superior portion of the left cerebellar hemisphere (Fig. 1). CAT scan confirmed the bullet's position (Fig. 2). Bilateral carotid and left vertebral angiography was remarkable only for minimal medial displacement of the left superior cerebellar artery, suggestive of swelling of the superior portion of the left cerebellar hemisphere.

The patient was treated for probable wound contamination and cerebral edema with parenteral oxacillin, chloramphenicol and dexamethasone. On this regimen the patient's lethargy, ataxia and nystagmus gradually diminished. Repeat skull radiographs obtained on July 12 revealed that, surprisingly, the bullet had migrated peripherally to a position near the inner table of the left occipital bone (Fig. 3). CAT scan confirmed this change in the bullet's location (Fig. 4). Craniotomy was performed on August 2, at which time the bullet was removed and superficial necrotic tissue debrided. Specimens taken during surgery failed to show any bacterial growth. Postoperatively, the patient experienced a transient increase in ataxia but improved sufficiently to be discharged on August 11.

Examination on September 29, 1978 revealed mild dysdiadochokinesis of the left upper extremity and slight nystagmus on left lateral gaze. Optokinetic responses

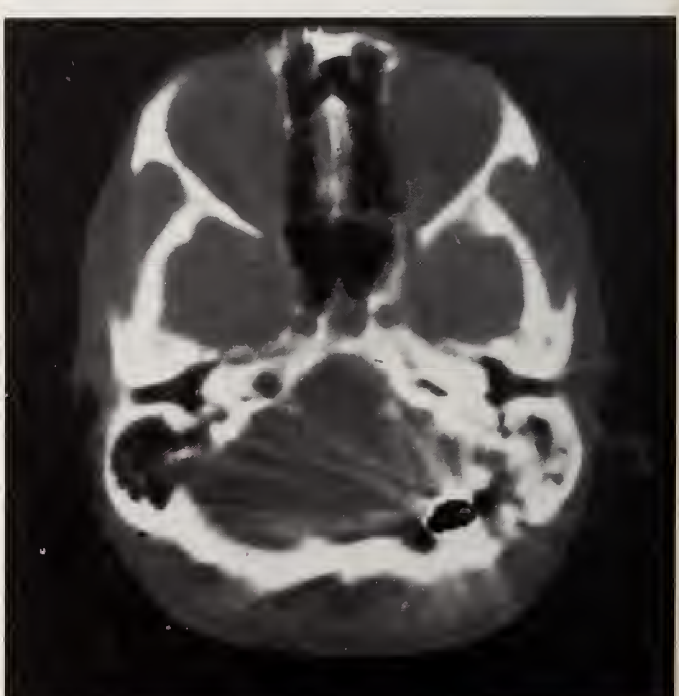


FIG. 4. CAT scan 17 days following injury. View is similar to that of Fig. 2(A). Bullet is now adjacent to entrance wound in occipital bone.

were normal. The patient is presently jogging more than one mile per day and his only complaint is of some "clumsiness" of his left arm.

Discussion

Although many authors have commented on the spontaneous migration of intracranial metallic fragments, this phenomenon has occurred infrequently. A World War I series described only one such case out of 1500 cranial gunshot wounds (1). In a series of 175 penetrating brain wounds in World War II, change in position of the fragments was found only four times (5). A more recent paper mentions only one such case out of 69 brain wounds (6).

Most authors agree that a spontaneously moving fragment is an ominous sign. In Wood's series, it only occurred in the presence of brain abscess (5). Martin and Campbell, reporting on patients injured in World War II, observed migration of fragments five times; in four cases, it was associated with brain abscess, in the other with a cerebellar hematoma (3). It was hypothesized that changes in position of metallic fragments could occur only if the fragment were located in a fluid-filled cavity or if it were being pushed by an adjacent mass. It has, therefore, been strongly recommended that all such fragments be removed and the surrounding necrotic tissue debrided.

However, it must be noted that all available reports derive from wartime series. Civilian cerebral gunshot wounds differ significantly from those incurred in war, primarily because the weaponry used results in bullets of lower velocity. The kinetic energy of a missile is related to the square of its velocity, and it is this energy that determines the extent of damage to cranial structures (8). Thus, in civilian injuries, there is generally far less cerebral tissue necrosis. It has, therefore, been thought, by some neurosurgeons, that civilian missile fragments may be left in place, especially if their removal necessitates an approach through uninjured cerebral tissue or if no hematoma is present (7). In the series of Raimondi and Samuelson which comprised 25 such patients, none developed significant adverse sequelae (mean follow-up period 31 months). This differs sharply from the statistics in various wartime series (9–11), thus documenting the relatively benign nature of retained civilian bullet fragments.

In our patient, the decision not to immediately remove the bullet was made with the above data in mind. Removal would have necessitated dissection through much of the left cerebellar hemisphere to approach the roof of the fourth ventricle.

The reason the bullet migrated is open to conjecture. It may be hypothesized that the bullet track, composed of softened necrotic tissue, offered less resistance to movement than did the intact brain. As shown by the CAT scan, there was no intracerebral hematoma or bone fragment to obstruct the bullet's path back to its portal of entry.

The immobilization of the patient's head in a position such that gravity assisted the bullet's progress was also a significant contributing factor. Not only was this immobilization the result of imposed bed rest, but in large part was caused by the nature of the patient's neurologic defecit. Any lateral movement of his head or attempt to sit upright was accompanied by severe vertigo, thus confining him to a supine position with his head directly forward.

Our case, in addition to demonstrating that a migrating bullet is not necessarily an ominous sign, supports the policy of avoiding potentially hazardous surgery in an attempt to remove all missile fragments. It also demonstrates the great value of CAT scanning in the assessment of patients of this type. The scan not only aids in determining the position of the bullet and bone fragments, but also can reveal many of the likely complications of these injuries (hematoma, abscess or hydrocephalus).

Acknowledgment

We are indebted to Dr. Morris Bender for referral of this patient.

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Trabecular Carcinoma of the Skin: Further Clinicopathologic and Ultrastructural Study

CHIK-KWUN TANG, M.B. AND CYRIL TOKER, M.D.

Abstract

We have added nine new instances of trabecular carcinomas to those previously reported (1, 3), a total of 17, to study them as a group. The patients usually had a lump of the skin with no other clinical or laboratory abnormalities related to the skin tumors. The excised skin tumors were sometimes interpreted as metastatic oat cell carcinoma, carcinoid or lymphoma. Electron microscopy that again demonstrated neurosecretory granules in three new tumors was found to be helpful in establishing the diagnosis. However, careful clinical evaluation continues to play an important role and familiarity of the characteristic histologic features is of utmost importance. Trabecular carcinoma of the skin is a low grade malignant tumor despite the fact that they are capable of recurrence and metastasis. Only one patient died from a tumor during this follow-up study. Four others died of unrelated causes. Six of those who survived, lived for more than five years. All survivors were free of disease at the last follow-up inquiry.

Introduction

Trabecular carcinoma is an unusual malignant tumor of the skin. Prior to Toker's original report of five tumors (1), trabecular carcinoma was diagnosed as metastatic oat cell carcinoma, metastatic carcinoid, or sweat gland carcinoma. Careful clinical search for primary tumors in these patients was negative and tumors did not develop in other sites during the follow-up periods. This led to the concept that trabecular carcinoma is a distinct type of primary skin tumor. The separation of this group of tumors from other tumors encountered in the skin and subcutaneous tissue was not entirely accepted (2), despite the characteristic trabecular pattern and rosette-like structures depicted, because the cell of origin could not be established by light microscopy and histochemistry. Subsequently, we studied three trabecular carcinomas with the electron microscope (3). The findngs of neurosecretory granules in all three tumors, in patients without tumors of neurocrest origin elsewhere, led us to suggest that trabecular carcinoma is derived from Merkel cells.

As a result of our continuous interest, we have accumulated additional cases of trabecular carcinomas of the skin for a follow-up study. This report describes the clinicopathologic and ultrastructural features of trabecular carcinomas.

Materials and Methods

A total of seventeen trabecular carcinomas were collected for analysis. Cases one through five were previously reported (1). Cases six through eight were studied by electron microscopy (3). For all cases, clinical information, including follow-up status, was obtained. The records of two patients (Cases 7 and 10) who were hospitalized at the University of Maryland Hospital were reviewed. Slides from all tumors were studied by light microscopy. Table I shows the clinical summaries of 17 patients. Tissues were available for ultrastructural study of three additional tumors. The method of fixation and sectioning was the same as that used for the previously reported tumors (3).

Results

Clinical Data: Ten of 17 patients were women and seven were men. All tumors occurred after 40 years of age with the preponderance in the sixth and seventh decades. The oldest patient was 92-years old. Eleven tumors occurred in the extremities; one in the buttock, and the remaining in the face. The majority of patients had subcutaneous lumps, some of which enlarged immediately prior to seeking medical attention. One patient

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From the Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland

Requests for reprints should be sent to Dr. Chik-Kwan Tang, Department of Pathology, University of Maryland School of Medicine, 22 South Greene Street, Baltimore, Maryland 21201.

(Case 2) had a flat pigmented lesion. Another had inguinal metastasis (Case 6). The duration of symptoms before surgery, in patients who recalled the development of their skin lesions, varied from two months to two years. Clinical manifestation in another patient (Case 11) was extraordinary. The patient was a 68-year-old woman who noticed a rapidly growing mass of the right upper arm shortly before biopsy. The biopsy was diagnosed as "metastatic oat cell carcinoma" but clinical investigation, including roentgenogram was negative for tumor elsewhere. Later, the mass became ulcerated and bled profusely, resulting in a forequarter amputation.

Clinical and laboratory investigation was negative for tumor elsewhere on almost all patients at the time of, or shortly after, the histologic diagnosis. One patient had adenocarcinoma of the prostate (Case 5) and another, villous adenoma of the colon (Case 4). The majority of patients were completely healthy and asymptomatic when their tumors were found.

Treatment and Follow-up

Fifteen out of seventeen patients had surgical resection of their primary tumors (Tables I and II). Of these 15 patients, four (Cases 2, 5, 10 and 15) developed recurrent tumors at the sites of previous surgery. For the recurrent tumors, treatment was either surgical removal only or irradiation only. Metastases in regional lymph nodes occurred in nine patients (Cases 3–6, 11 and 14–17), and were found before, at the time of, or after the primary sites were discovered. The metastases were treated by lymph node dissection only, lymph node dissection followed by irradiation, or irradiation followed by lymph node dissection. Five other patients (Cases 1, 8, 9, 12, and 13) had neither recurrence nor metastasis. One patient (Case 7) was lost to follow-up after the initial surgery.

The remaining two patients (Cases 11 and 16) were treated by irradiation after the diagnosis of trabecular carcinoma was established by biopsy. Case 11 eventually underwent a forequarter amputation for profuse hemorrhage from the tumor, following irradiation. One patient had lymph node metastasis at the time of diagnosis and the other patient, seven years after the initial diagnosis.

Of the six patients who received irradiation, two (Cases 10 and 16) responded, with disappearance of tumors; and three (Cases 5, 11 and 15) did not. The remaining patient (Case 4) received irradiation after the metastatic tumor was removed.

Regardless of the method of treatment, six patients survived more than five years (Table I); most were still alive at the time of this report. So were those who were followed for less than five years. Only five patients died during the period of follow-up. Four died of unrelated causes. Only one patient died from a tumor (Case 5). Two patients have not returned to the hospital for follow-up examination since surgery. One patient was lost to follow-up. Table II shows the follow-up status in relation to different types of treatment.

Pathologic Observation

Grossly, most of the tumors were small, usually less than 3.5 cm. in greatest dimension. The tumors were homogeneously yellow-white, firm to hard, in the subcutaneous tissue, but compression of the epidermis could be seen with or without ulcerations (Fig. 4) (3). The tumor of Case 11 was extraordinarily large. It was yellow, somewhat lobulated with a sharp periphral margin, but with two separate similar tumor masses.

The histologic features were described in detail in the two previous communications (1, 3). Eight of the nine additional tumors showed basically the same histologic features although squamous component was observed in Case 17. The characteristic features included trabecular pattern, rosette-like circular structures, serpiginous clefts and small tumor cells with scanty cytoplasm and relatively uniform nuclei. Mitoses varied from tumor to tumor. Lymphocytic infiltrate (Fig. 1A) was occasionally seen and, in one instance, was pronounced. Occasionally, the tumor cells were spindle-shaped (Fig. 1B), histologically indistinguishable from those of oat cell carcinoma. In Case 15, the primary tumor was typical of trabecular carcinoma but the tumor became diffuse when found in the regional lymph node (Fig. 1C), closely resembling lymphoma. The last tumor (Case 11) demonstrated a diffuse pattern in many areas, reminiscent of that of a diffuse lymphoma (Fig. 1D), with necrosis. Only focally were circular structures present (Fig. 1D).

Electron Microscopic Observation

All three new tumors (Cases 9, 10, and 11) subjected to electron microscopic studies showed small neurosecretory granules (Figs. 2, 3, 4), although they were less numerous than those found in Cases 7 and 8. In addition, trabecular structures were observed in Case 10, corresponding to those seen by light microscopy. In Case 9, cytoplasmic processes resembling microvilli were conspicuous, suggesting glandular differentiation. The tumor cells of Case 11 were considerably smaller and contained only a few cytoplasmic organelles (Fig. 2), closely resembling lymphocytes. However, neurosecretory granules and definite intercellular junctions were present (Figs. 3, 4). Some cells in the same tumor had the tendency to form circular structures (Fig. 2). Intercytoplasmic fine fibrils were found and like those observed previously (3), were usually in small bundles but occasionally formed a large concentric configuration. Other cytoplasmic structures such as mitochondria, rough endoplasmic reticulum (ER), and free ribosomes did not demonstrate specific changes.

TABLE I

Clinical Summaries of 17 Patients with Trabecular Carcinoma of the Skin

Case No.	Age	Sex	Site	Duration Before Surgery	Clinical Manifestations of Tumor	Other Significant Clinical Data	Size of Tumor	Treatment	Local Recurrence	Metastases	Follow-up	
											Duration	Status
1*	65	F	Forearm	3 months	Firm, nontender mass	None	1.0 × 0.5 cm.	Surgical removal	None	None	8 years 3 months	NED
2*	70	F	Leg	Unknown	Flat, pigmented lesion	None	1.5 × 0.5 cm.	Surgical removal	Twice. Both surgically removed, 8 & 31 months	None	10 years	†NED
3*	65	F	Face	1 year	Lump, enlarged rapidly PTA	Esophageal stricture	1.5 × 1.0 cm.	Surgical removal	None	Submaxillary lymph node 3 years after surgery	10 years	Lost to follow-up since reported)
4*	76	M	Lip	4 months	Rapidly growing tumor of lip	Villous adenoma of colon	2.5 × 2.0 cm.	Surgical removal of primary; bilateral neck dissection, followed by irrad.	None	Bilateral cervical lymph nodes	3 years 6 months	Died of hemorrhage from the colonit tumor
5*	75	M	Buttock	2 years	Enlarging mass of right buttock	Adenocarcinoma of prostate, myocardial infarction	3.0 × 2.0 cm.	Surgical removal of primary; irrad. to recurrent tumor	Rapid, massive at surgical site	Extensive in inguinal node	2 years 3 months	Died of carcinomatosis
6**	72	F	Leg	Unknown	Enlarged inguinal lymph node found on PE, followed by discovery of primary	Hemoptysis, general anasarca, dyspnea, cough and fever	1.5 × 1.0 × 1.0 cm.	Surgical removal	None	lt. inguinal node	5 months	Died of congestive heart failure. No autopsy
7**	76	M	Thigh	Unknown	Lump	Abnormal uptake in hilum of lungs, nature unknown	0.6 cm. in diameter	Surgical removal	?	?		Has not returned for follow-up since surgery
8**	92	F	Cheek	Long duration	Rapidly growing tumor shortly prior to surgery	None	3.5 × 3 cm.	Surgical removal	None	None	6 months	Died of unrelated disease
9	48	M	Arm	More than 2 months	Rapidly growing tumor developed over the site of an A-V fistula (For renal dialysis)	Renal disease	5.0 cm.	Surgical removal	None	None	1 year 5 months	NED
10	74	F	Cheek	Months	Cheek lesion gradually enlarging over months	None	3.5 × 2.2 × 7.5 cm.	Surgical removal of primary; irrad. for recurrence	At surgical site	None	7 months	NED

11	68	F	Arm	Unknown	Ulcerating, fungating mass, no tumor elsewhere	None		Irrad. forequarter amputation	?	Axillary lymph nodes and soft tissues	6 months	Has not returned for follow-up since surgery
12	63	M	Gluteal region	Several months	Lump	Aortic aneurysm	3 cm. in diameter	Surgical removal	None	None	4 years	Died of cardiopulmonary problism 1977; no tumor
13	67	F	Cheek	Unknown	Lesion on cheek	None	1 cm. in diameter	Surgical removal	None	None	1 year	NED
14	Middle-aged	M	Knee	6 months	Nodules in popliteal area	None	0.7 cm.	Surgical removal	None	Lymph node, upper thigh	7 years 6 months	NED
15	61	M	Digit	Unknown	Growing painful mass	None	1.5 cm. in diameter	Surgical removal of primary; irrad. to axillary, followed by lymph node dissection	3 months after 1st excision	Axillary lymph node	5 years 7 months	NED
16	46	F	Pretibial area	Unknown	Plaque-like induration	None	2 cm. in diameter	Biopsy followed by irrad. to primary; lymph node dissection	None	Inguinal lymph node, 7 years after diagnosis	10 years	NED
17	71	F	Foot	Unknown	?	?	Less than 2 cm. in dia.	Surgical removal	?	Lymph node		Lost to follow-up

* Reported previously (1)
** Reported previously (3)
† NED = No evidence of disease
IRRAD. = Irradiation

TABLE II

Treatment and Follow-up Status

		FOLLOW-UP STATUS				
	No. of Cases	* NED		† DOD	‡ DOC	§ FU not available
Treatment		<5 yrs.	5 yrs.	<5 yrs.	<5 yrs.	
Surgical removal only	11	2	4		3	2
Surgery or biopsy and irradiation	6	1	2	1	1	1
Total	17 =	3	6	1	4	3

* NED = No evidence of disease
† DOD = Died of disease
‡ DOC = Died of unrelated cause
§ FU = Follow-up

Discussion

The features observed in this series indicate that trabecular carcinomas, as a group, are unique skin tumors. Clinically, patients with trabecular carcinoma of the skin are over 40 years of age. The clinical manifestation is nonspecific. The presence of a lump can be interpreted as many different conditions, such as basal cell carcinoma, skin appendage tumor, etc. None of the patients exhibited any evidence to suggest that trabecular carcinoma is part of a syndrome. The other medical conditions encountered in a few patients (Table I) were apparently unrelated.

The misinterpretations of trabecular carcinoma reflect,

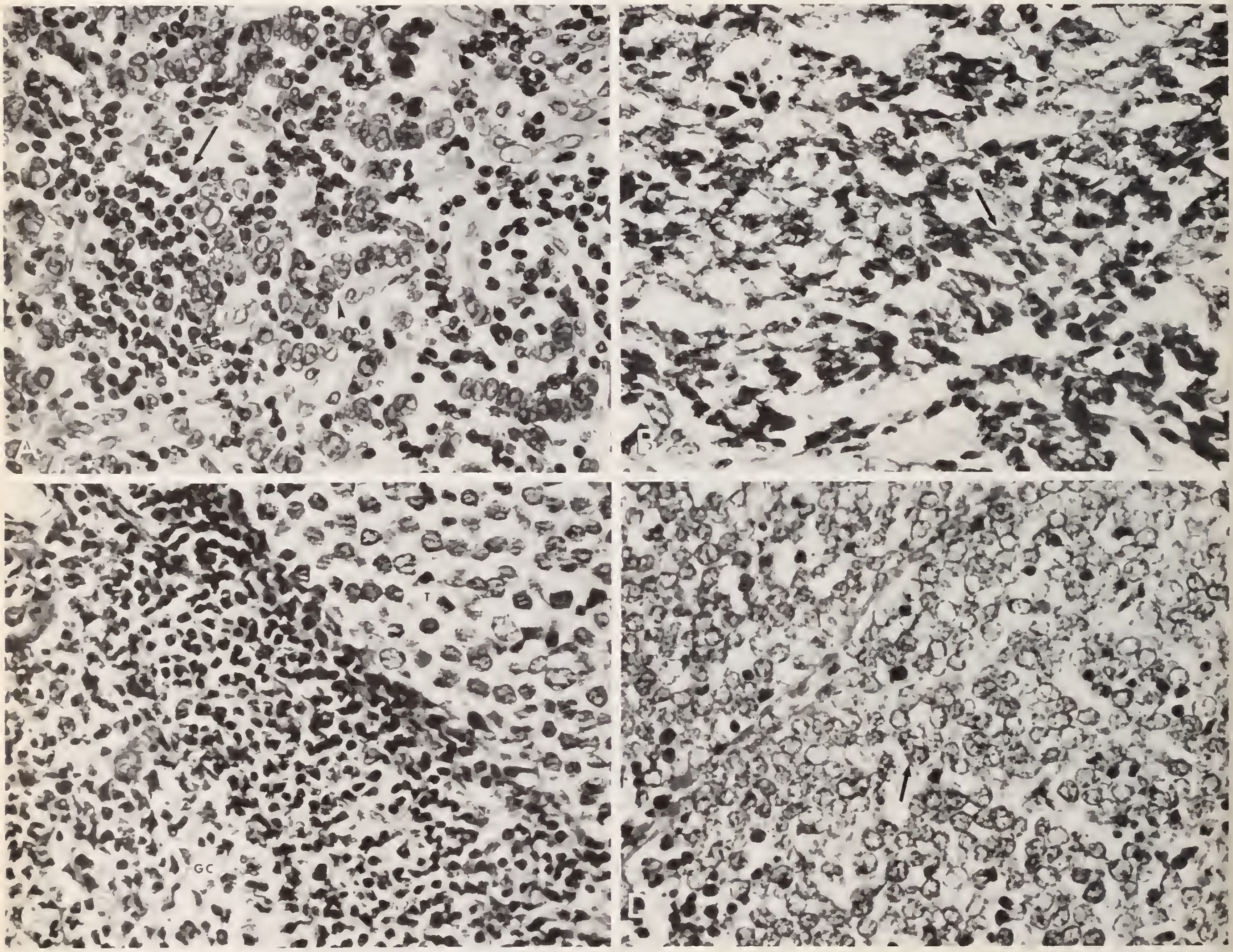

Fig. 1. Features of trabecular carcinomas that can be confused with other tumors: A) *Case 9.* Marked lymphocytic infiltrate (arrow) in tumor proper, that may mislead pathologist to arrive at a diagnosis of lymphoma. Typical trabeculae (arrow head) are seen, a feature not seen in lymphoma. B) *Case 10.* Focal areas of spindle cells with hyperchromatic nuclei (arrow) are observed in an otherwise typical trabecular carcinoma, that may be mistaken for oat cell carcinoma. C) *Case 16.* The diffuse tumor cells in the lymph node (T), unlike those in the primary diagnostic of trabecular carcinoma, may be interpreted as diffuse histiocytic lymphoma. However, the tumor cells are different from those seen in an adjacent germinal center (GC). D) *Case 11.* A diffuse pattern of tumor cells with scanty cytoplasm and vesicular nuclei again suggests lymphoma. Only occasional rosette-like structures (arrow) are found (A–D: ×500).

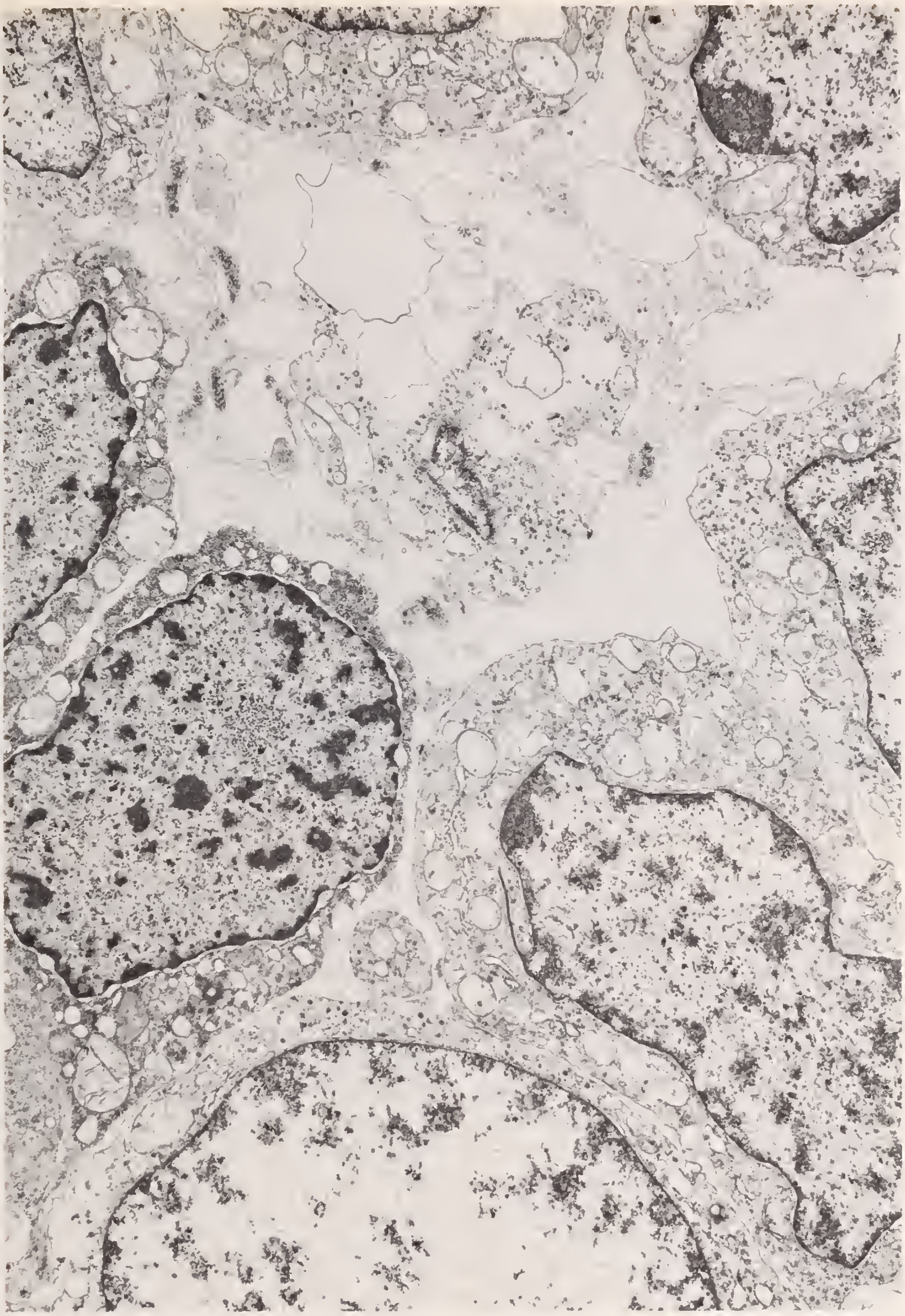

FIG. 2. *Case 11.* Electron micrograph showing the tendency to form a rosette-like structure (×6,750).

to a certain extent, that the histologic features of trabecular carcinomas may resemble those of other tumors. Metastatic carcinoid tumor is a common differential diagnosis that is most difficult to exclude because both tumors have trabecular structures on light microscopy and neurosecretory granules on electron microscopy. Peripheral palisading of tumor cells seen in carcinoid were not observed in our series of trabecular carcinomas.

Careful clinical investigation is of utmost importance in this situation. The diagnosis of metastatic oat cell carcinoma is suggested by the appearance of individual tumor cells, that is, scanty cytoplasm and hyperchromatic nuclei. Rosette-like structures and serpiginous clefts are not the features of oat cell carcinoma. Diagnostic problem may arise when tumor cells of trabecular carcinoma are diffusely distributed in a pattern closely

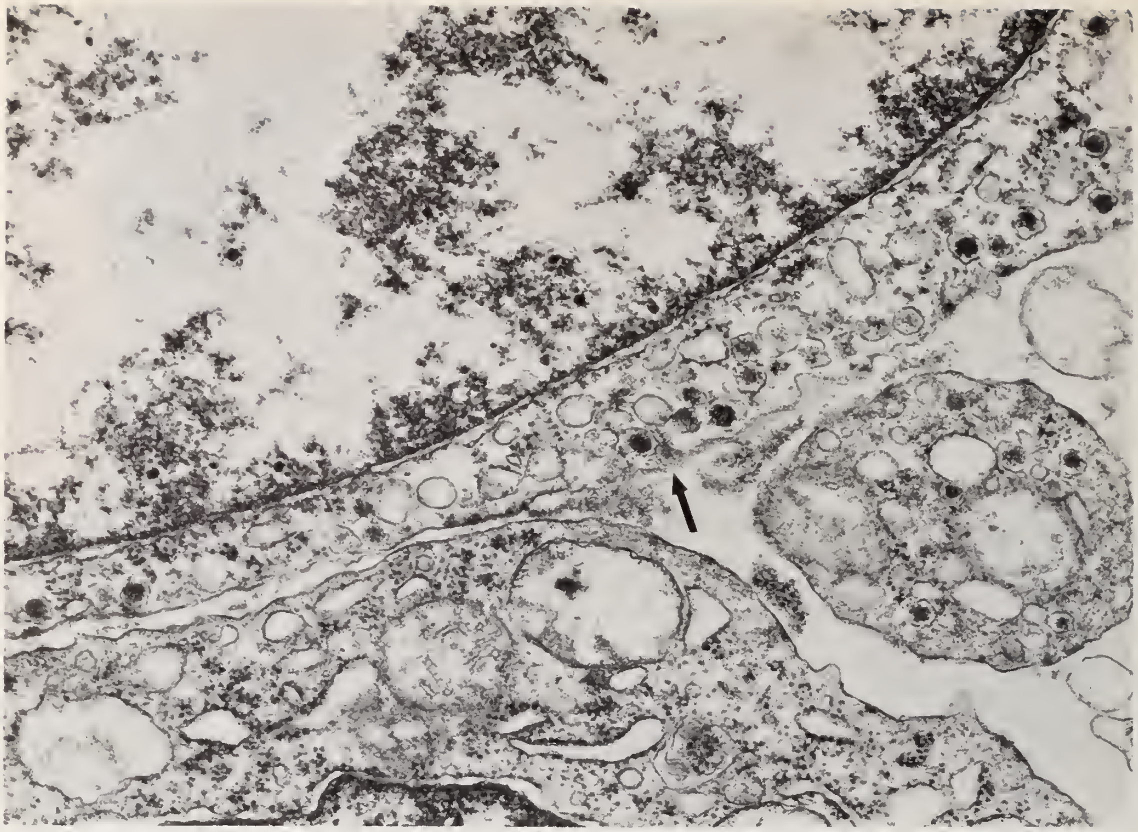

FIG. 3. *Case 11.* Many neurosecretory granules (arrow) present in tumor cells. Rough ER, slightly swollen mitochondria and free ribosomes are observed (×23,250).

resembling that of a malignant lymphoma, particularly reticulum cell sarcoma (histiocytic lymphoma). For instance, in Case 11, metastatic oat cell carcinoma was originally considered but excluded by a negative clinical investigation. In view of the extraordinarily large size with the involvement of axillary lymph node and the diffusely distributed tumor cells, lymphoma was strongly suspected. Rosette-like structures, however, were found in some areas, raising the possibility of trabecular carcinoma. The latter diagnosis was supported by the ultrastructural findings of neurosecretory granules and intercellular junctions both of which are features against the diagnosis of lymphoma. Scanty cytoplasm and a few organelles suggest that the tumor cells are rather primitive.

In the event that the distinction between sweat gland carcinoma and trabecular carcinoma cannot be made, ultrastructural studies may provide further information to solve the diagnostic problem derived from light microscopy. The significance of lymphocytic infiltration frequently seen within or adjacent to tumor is not known.

Trabecular carcinoma is capable of recurrence and metastasis. Usually, metastasis occurs in regional lymph nodes and may, on occasion, be the first clinical manifestation.

Elliptical excision with adequate margins of resection appears to be adequate treatment for trabecular carcinoma without lymph node metastasis. The recurrence at surgical site or metastasis in lymph node can be treated by further surgical removal. Irradiation produced favorable result in two patients but not in three others.

Despite the capability for local recurrence and metastasis, trabecular carcinoma does not appear to be a highly malignant tumor. There have been at least six, five-year survivors–all of whom were free of disease at the last follow-up inquiry (Table II). Four out of these had metastasis in regional lymph nodes, either at the time of diagnosis or several years after. The favorable outcome of these six patients might be related to the small size of the primary tumors or might reflect the low grade malignant potential of trabecular carcinoma. Five patients died within five years, four, of unrelated diseases. Three patients were lost to follow-up.

We have broadened our knowledge of trabecular ca cinoma of the skin. As a group, the patients generally had a consistent pattern of clinicopathologic and ultrastructural presentation. Careful clinical evaluation continues to be important in establishing the diagosis and in managing patients with trabecular carcinoma. The histologic features, though characteristic, do at times overlap with those of metastatic carcinoid, oat cell carcinoma, primary sweat gland carcinoma, and lymphoma. Electron

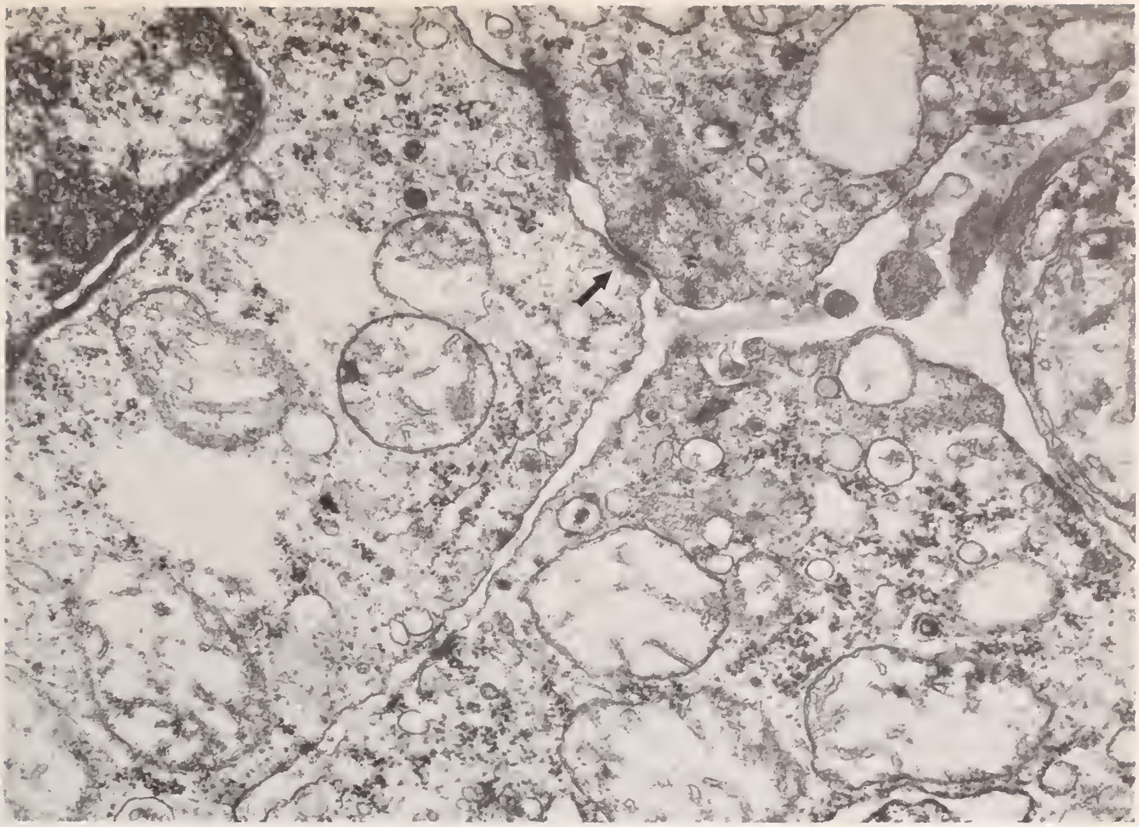

FIG. 4. *Case 11*. Intercellular junctions (arrow) are well-developed in some tumor cells. Nonspecific cytoplasmic filaments are present (×23, 250).

microscopy can be helpful in supporting the diagnosis but familiarity of the characteristic histologic features is of primary importance.

Addendum

Case 9: The patient developed metastasis in the ipsilateral forearm two years after surgery.

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Clinical Perspective in the Treatment of a Family with Folie À Trois

RUTH FEIBEL, M.D. AND DAVID SCHULMAN, M.D.

Abstract

This paper includes a review of the significant literature about the clinical syndrome Folie À Trois plus an indepth presentation of a family in which the mother and two daughters were afflicted with varying psychopathological degrees of this disorder. The therapeutic strategy involved working with all family members individually and, when possible, in a group. The "healthy" father was actively involved in this process which was accomplished through the utilization of a well-integrated multidisciplinary team approach. A psychodynamic explanation of the clinical data is offered.

The occurrence of related psychotic symptoms shared by two or more persons is termed Folie à Deux or shared paranoid disorder (Draft DSM-III). It was described by Berlyn in 1819 and the term folie à deux was first used by Lasegue and Falret in 1877 (1). Montyel (1881), Gralnick (2), Ropschitz (3), Pulver and Brunt (4), and others have added to the understanding of this pathologic entity. It was considered to be a curious and rare entity and aroused the interest of many. Wolf in 1957 (5) noted that few, only 15 cases of Folie à Trois (shared delusions in three associated persons), have been reported in the English literature. The same is maintained in 1961 with another publication of a Folie à Trois (6). Floru in 1974 mentioned 267 articles written on the subject of induced psychosis (7). Simmonds and Glenn in an article of folie à deux in a child and parent mentioned that folie à deux in children has rarely been discussed in the literature (8).

Dewhurst and Todd suggested that the following criteria be present before a definite diagnosis is made: a) the presence of positive evidence that the partners have been intimately associated, b) the presence of a high degree of similarity in the general motif and delusional content of the partner's psychosis, c) the presence of unequivocal evidence that the partners accept, support and share each other's delusional ideas (9).

Case Report

Mrs. M. a 40-year-old black woman and her two daughters, S. age 14 and E. age nine, were remanded by Family Court to our hospital for psychiatric evaluation. They came to the attention of the Family Court because of the girls' prolonged school absenteeism. The mother, a teacher's assistant, lived with her husband and daughters and worked while attending college courses in preparation for her M.A. degree. About two years ago, she began to display peculiar behavior and began expressing strange ideas. She asked her husband to leave the home, became concerned about her daughters' schooling and dropped out of college herself. She claimed that her daughters were too old for school, that "school is a mess," and didn't allow them to continue to attend classes. She rejected her husband, forbade him to enter the house, and she and her daughters refused to speak to him anymore. They secluded themselves in the home and went out only for minimal shopping.

When brought to the emergency room and later on the wards, all three refused to respond when called by their names. They denied their identity and each of them maintained that the father was not related to them. All three, individually claimed that they did not come from the United States, but that they came from the "other side" and spoke of being persecuted "here in America because we are negro." They denied being "black" and criticized the term of "white." "You are pink not white, only God is white." School was unacceptable because "young men mess up with young ladies." According to each of them, E. was "a young lady of 18 years of age." S., the 14-year old, was "in her twenties, a young woman." Both daughters, therefore, were not in need of any further education. These distortions and most of the others were shared by all three family members and repeated to staff members on many subsequent interviews.

They were hospitalized and placed in three different wards, Mrs. M. in the adult female ward, S. in the adolescent female ward, and E. in the childrens' unit.

From the Department of Psychiatry, Mount Sinai Services, City Hospital Center at Elmhurst, Elmhurst, N.Y.

Requests for reprints should be sent to Ruth Feibel, M.D., 109-23 71st Road, Forest Hills, N.Y. 11375.

None admitted to any past psychiatric history. According to her own account, Mrs. M. was the only child of her mother's first marriage. She never knew her father who was said to have died of unknown reasons at the time that she was born. Her mother remarried when Mrs. M. was six-years old and had four other children in her second marriage. The relationship between Mrs. M. and her step-father and her half siblings was described as "perfect." She denied any difficulty during her past and described herself as a good student with good marks and claimed to have had rewarding experiences in and out of family.

When Mrs. M. was 18-years old, she met Mr. M., then 22-years old. Both were working, she in a school and he in a small office. After some years of marriage she changed her work place in an attempt to improve her situation financially and professionally. Six years ago, after a period of staying at home "because she was tired," she resumed her occupation but only for one and a half years and then enrolled in a college program. A year later, she stopped both work and studies. Her relationship with her husband became strained and she accused him of being oblivious to his own educational needs and of being interested only "in making money." In 1976, although Mr. M. claimed that he opposed it, they were divorced. Following that, Mr. M. still continued to visit them weekly and provide financial support until about a year prior to their hospital admission when they refused to let him into the house.

On admission, Mrs. M. appeared her age, was pleasant looking, well built, well groomed and neat. When spoken to, she became hostile and angry. Her answers were short and biting. She would have a faint disdainful smile after each sarcastic charge. She accused the hospital staff of being ignorant, malevolent, wicked and of interfering with their lives. She said "I was born in the other hemisphere, I am not divorced, I have a husband who is here with me. I don't know Mr. M., I have two daughters, neither named S, nor E." Her orientation was intact. Her mood changed from angry to neutral or inappropriately flat.

Mrs. M. described the early history and development of both her daughters as "normal." The only objective available information was about S's school performance. She was not sociable, was often verbally abusive and functioned academically in the low-average range.

S., the older daughter, is a slim girl who appeared at the time of admission to be unkempt and disheveled. She was withdrawn, did not acknowledge the interviewer's greetings and outstretched hand. She avoided eye contact, turned her back and refused to answer when addressed by her name. The name she wanted to be called was "Angel;" she didn't answer questions in reference to her family or herself saying, "I don't know you, it's none of your business." She refused to attend school classes and repeated "I am too old to go to school. In school they mess you up, you know what I mean. I am not from here, I am from the other side." Mr. M.'s attempts to visit with her were ignored or rejected and she would say, "Mr. M. is not my father, I don't know him." At night she often wandered aimlessly around the ward.

The younger daughter E. appeared well groomed and neatly dressed. When addressed by her given name she became hostile and stated that this was not her name, but accepted the adopted name of "Joy." She denied that M. was her family name and claimed not to know any Mr. M. She stated "the real father will come to take us out of this hospital." Food was refused because "it is polluted." She does not belong to America but "to the other hemisphere." She spoke in anger and her face would take a special manneristic trait encountered also in the other two. She insisted that she was 18-years old, "a young lady" and didn't have to go to school. She wanted to get married "to her chosen mate, the one from the other hemisphere." She reluctantly admitted that mother shared with her and her sister all this knowledge-knowledge received by mother from God who showed himself to her.

Hospital Course

Throughout the early days of her stay Mrs. M. maintained her hostile attitude and delusional thinking. She was placed on progressively increasing doses of Haldol which initially she had refused. Shortly after admission, she appeared in Court for a hearing and was returned to the hospital for further treatment. At that time she was withdrawn, did not answer when called by name, and did not follow directions. Social interaction with the other patients was minimal.

Early during the M.'s hospital stay, Mr. M. was seen and evaluated. It was clear that he was emotionally involved with and attached to his family even though he had been so vigorously rejected and ignored by them. Mr. M. was encouraged by his social worker as part of an initial integrated plan to continue to come and visit the family on a regular basis.

A therapeutic plan gradually evolved that was designed first to reconcile the parents, if possible; second, when appropriate, to place the children in residential treatment facilities. As time passed, Mrs. M. became more cooperative, took her medication, related more to the other patients and staff. She began to accept and tolerate the visits from her husband quite well. Idiosyncratic thoughts diminished and she appeared less angry and more depressed. She gradually accepted returning home to live with her husband as well as treatment for herself at an out-patient facility after discharge from the hospital. In time, she began to see the advantages of having her daughters treated and agreed to have them placed outside of home as a therapeutic measure. Mrs. M. was discharged after six weeks with the understanding that she and Mr. M. would resume living at home together. By this time they were getting along much better. She visited the outpatient department and was maintained on Haldol 40 mg daily.

S. continued to be uncooperative and withdrawn for a long time. She was mostly angry and irritable. She persisted in her delusional thinking and did not partake in any ward routine or school activity. On a number of occasions she was found drinking her urine "to undo the effect of the medicine" and was caught smearing her hair with feces "to keep it shiny." Slowly her behavior improved, she was less delusional and showed more adaptive attitudes. She interacted better with her peers but continued to be unreachable in individual therapy for a long period. She was treated pharmacologically with Haldol that was reduced because of side effects to a maintainance dose of 1 mg daily.

E. improved rapidly in her attitude toward the other children on the ward; she enjoyed playing with them and acted in an appropriate age manner despite her claim to be "a young lady." She repeated, but less vigorously, the fixed ideas about "the other hemisphere" and "mates from the other side." In school she functioned at her age and enjoyed the praise of her teachers. However, in individual treatment sessions she reported that she hated school. In time she accepted Mr. M. as being her father. Whereas episodical abdominal pain during the first month of her hospitalization was interpreted by E. to be evidence of the onset of menarche to support the delusion that she was older, later she didn't mention it anymore. Sexual subjects aroused her interest and she was provocative on the ward. She was maintained on Thorazine 50 mg daily.

Treatment

The accepted treatment for a psychosis of association is to separate the dominee from the dominant partner. In this case, we decided that maintaining some physical and emotional contact between family members might hasten their remission. A similar approach was taken by Wolff (5) who cited Ascher's statement that enforced separation of the dominant partner from the others was not helpful in all cases. We hoped that the knowledge of the physical integrity and well being of each would help mother and daughters to experience some sense of safety and confidence in those who were to help them. We gave them the opportunity to be together, periodically, once a week. In line with such a treatment plan, the team's interventions were designed to help mother and daughters maintain their attachments to each other, supporting the positive healthy aspects of their relationship and identifying the inappropriateness of the psychotic features that bound them together. Mrs. M's role as a mother was acknowledged and her ability to influence her children was used constructively. During Mrs. M's hospitalization, a plan for regular visits between mother and daughters was arranged with the social worker joining them to monitor and provide supervision of the group. After Mrs. M's discharge from the hospital, weekend passes for visits at home for both girls were issued with the provision that the father would be present. Mr. M. was encouraged to be involved with his family and actively participated at their meetings. The help he got from the treating team social worker gave him the support he needed in the relationship with his wife and daughters and reinforced his self-esteem. However, the return from a weekend pass was followed in both girls by regression; they became more belligerent and repeated their delusional thoughts. E. hid feces in her cabinet's drawer and when questioned about it got sulky and later mentioned that it is healthy for the hair, "don't babies play with feces and isn't their hair shiny?" S. reverted to her aloofness, hostility and mannerisms. It became apparent that S., the older daughter, took over the mother's domineering role toward the younger sister. The passes were reduced and issued only for specific purpose as a well-structured day program with the father.

The results were immediately noticeable for E. Her testing attitude diminished, she showed healthy curiosity, and began to grasp new information. As long as she was subjected to mother's and sister's influence, the misconceptions about the world around her were reinforced. When offered the occasion to clarify these false beliefs, she keenly appreciated the opportunity and asked to be seen more often in treatment sessions. In her drawings she appeared to gain control over the psychotic images and became more capable of expressing outer realities. She agreed with the plan to be placed in a residential treatment center (RTC) and was pleased when after five months of hospitalization an opening was available for her in one of these treatment centers.

The same plan was established for S. but she needed more time in the hospital before being ready for a RTC. Only after E. left the hospital did S. allow herself to verbalize her feelings and doubts: "Mother was sick, she made us sick too."

Since each member of the family was in a separate ward, the treatment was conducted by different hospital staff members and the meetings were coordinated by the social case worker with the help and supervision of the attendings on the wards.

The treatment encompassed individual psychotherapy, milieu therapy and group sessions. E. got additional art therapy.

Medication with antipsychotics was started immediately for Mrs. M. Because of extrapyramidal symptoms (EPS) she received additional anti-parkinsonian drugs.

She was maintained on Haldol 40 mg daily. At the beginning of E's hospitalization she was not given medication; but because of periods of poor impulse control and increased anxiety, Thorazine was given on a regular basis. She reacted favorably and was maintained on Thorazine 50 mg daily. S. developed side effects and Haldol was reduced to 1 mg daily, and later during her hospitalization S. was treated with Imipramine 200 mg/day.

Discussion

It was agreed by most authors (1-5) that the state of Folie à Deux or "shared madness" occurs under exceptional conditions in which one person, the more active dominant one, develops the delusion that is then imposed upon the more passive and initially healthier one. The persons involved live within a secluded existence for a prolonged period of time, sharing hopes, expectations and fears. They are isolated from the outside world and its influence. The delusional system is the expression of apprehensions originated in events from the past and of promising hopes for the future. The strong emotional association together with prolonged physical closeness is based on emotional interdependence. The delusions once communicated are reinforced by the other or others. Only separation from the principal partner allows for the reintegration of the weaker and more dependent one. (10).

Four subgroups of Folie à Deux have been described in the literature. Folie imposée, Folie simultanée, Folie communiquée and Folie induitée and, although controversial, are still used (10). The value of such subgroups was contested by many (8,10) and thought to be neither meaningful nor helpful. Folie simultanée and induitée have been negated of having any practical purpose and described as redundant.

Folie simultanée is the subgroup in which the factor of transmission is described as either nonexistent or only negligible. The delusions happen to develop simultaneously but independently in the two subjects because of morbid predisposition, prolonged intimate association and same precipitating trauma acting on both. This condition is not likely to subside with separation of the two individuals.

Folie induitée, meaning induced, is found in hospitals and consists of the addition of new delusions to an existing psychosis as a result of association with other patients.

Folie imposée, in translation denoting enforced or compelled, is the syndrome usually given the name Folie à deux.

Folie imposée was described by Lasegue and Falret (1877) in which one of the individuals is the more active partner, is more intelligent and gradually imposes his psychoses upon the passive partner. The induced partner, although deluded, is not really psychotic in the strict sense of the term and could return to normalcy after separation from the active member. Suggestion and intimacy are important elements in this relationship. Folie communiquée was described by Marandon de Montyel (1881) in which the receptor accepts the delusions only after prolonged resistance and in which psychosis persists even after the partners have been separated. Predisposition and hereditary constitutions are said to play a major role.

The stability of the psychosis affecting the weaker partner that will determine whether it is a Folie imposée or Folie communiquée is based, according to Dewhurst and Todd, on variables that hardly justify this differentiation. Those variables are: the duration of the psychosis, the nature of the delusion, and the suggestibility of the induced. (9).

In our case, the exposure to the mother's delusions was the same for both daughters. Both appeared suggestible and dependent. Both maintained an excessively close psychologic relationship with the mother, and used the mother as an auxiliary ego with regard to the regulation of their impulses and self-esteem.

E. James Anthony believes that Folie à deux can be viewed as a developmental failure in the process of separation-individuation, as an unresolved symbiotic relationship in which the mother requires the acceptance of her delusions as a test of loyalty. He considers that passive, fearful, impressionable children might be more prone to become partners in a delusional system, more so if they present cerebral troubles (11).

On psychological tests, both daughters had signs of organic dysfunction. E's visual motor skills were two years below her chronologic age. S. showed clear evidence of organic dysfunction with marked inability to perform on perceptual motor items that placed her developmentally in some areas five to six years below her chronologic age.

The acceptance of the psychotic delusion by both girls can be viewed as a consequence of emotional and physical isolation and as an attempt at salvaging a relationship with the mother. In view of learning theory, the induced partner has learned to avoid the hostility and rejection and is conditioned to accept the thinking of the dominant partner.

Marandon de Montyel expressed that the content of the delusion is determined by the social climate and the prevailing ideas of the time (3).

This view was confirmed in our case with the heightened public interest in black affirmation, sexual liberation, religious commitments, interests in education and ecology that were reflected in the delusional system of the M. family. Their ideas revolved around themes of their origin, the "black hemisphere," the religious belief of predetermination, and the fear of precocious sexual interest in the daughters. They had the feeling of being misunderstood in the community and mistreated in school.

The alienation might have originated in Mrs. M's fear over her own sexual impulses, her fear over losing control, and her fear of losing her hold on reality. Hartmann and Stengel, cited by Dewhurst and Todd, stress the importance of the inducer's dominance on the induced as an attempt to keep in touch with the exterior world at a time when he or she feels threatened with isolation by loss of contact (9). The distortion of the daughters' ages seemed to have served the purpose of keeping them home with the mother so that she wouldn't be left alone through her most disturbed period.

Mrs. M's frustration and inability to function at the expected level in college was an additional element. Whether this was a precipitating event or whether the schizophrenic process took its course and interfered with her later academic activity is hard to determine. In most reported cases, the inducer is the wife or mother. The dominant woman tries to instill her beliefs into the members of her family. Apparently Mr. M. being more intact, was less frequently at home, and thus was less under the influence of his wife. He resisted and was described by his wife and daughters as "stupid," "dumb." Mrs. M. then rejected him in anger. Similar cases were described by Monbrun Kepner who noted the need of these women to convince others of their beliefs in order to keep hold on the external world (12). The men were described as weak and timid with a deep sense of guilt. Although he did not share the delusions, Mr. M. resembled this picture very much. He was strong enough to withstand the delusions but was not strong enough to support his wife and children and to prevent their deterioration. The girls felt his inadequacy and resented it–voicing their terrible anger towards him by negating their relationship as their mother had done.

The older daughter was more predisposed to develop a psychotic delusional system with the mother. According to Waltzer who cites Deutsch (13), the recipient never accepts ego alien material and the delusional ideation must be similar to the unconscious fantasies and fit the defense mechanisms of the secondary partner. The psychological tests on S. confirmed the diagnosis of schizophrenia, paranoid type. The additional finding of organic features indicated a vulnerability that compounded the picture and facilitated the process. Her psychosis and course of illness suggests the subtype of Folie communiquèe.

E., the younger sister, took over the delusional system because she was unable to evaluate and counter those beliefs. She had no discriminatory abilities because of her age and reduced knowledge. She needed to be accepted, approved of and supported by her mother. The model of the mother that she tried to identify herself with did not allow for any critical thinking. The psychological tests revealed a circumscribed delusional system in an organically vulnerable child. The diagnosis was transient psychotic episode, Folie à Trois, subtype Folie imposée.

Folie à deux is an entity that we think may occur more frequently in many other forms but may go unrecognized unless it interferes with a person's work, school or community functioning.

In this case, the treatment involved a multidisciplinary team approach that was flexible with periodic reassessment and readjustments according to the patients' responses. It used a spectrum of techniques, including individual psychotherapy, group psychotherapy, psychopharmacology, milieu therapy and activity therapy.

The prognosis for all members remains guarded, and close followup will be necessary for a longer period of time.

Summary

This is a case presentation of a Folie à trois in a family of four in which the mother and her two daughters were affected. They expressed the same delusional beliefs, showed the same rejection and lack of interest in their environment, and the same hostility toward the people called upon to help them.

The mother, the dominant member in the trio, was the first to reintegrate enough to be discharged from the hospital. She was a schizophrenic, paranoid type with delusions of persecution and hallucinations of a mystical nature.

The older daughter who was diagnosed as schizophrenic, paranoid type, maintained her delusions the longest. She took over the domineering role toward the younger sister and during her hospitalization regressed the most.

The younger daughter improved after she was removed from the influence of the domineering partner, first the mother, and then the sister. It was noted that the improvement occurred immediately upon hearing that she would be placed in a residential treatment center. The anticipated separation from the psychotoxic influence was sufficient to mobilize her strength and to improve her level of functioning. The treatment involved a multidisciplinary team approach and followed the previously described steps.

A one-year followup study finds one girl, placed in a residential treatment center, functioning very well; the mother rejoined her husband and is doing much better; and one daughter is still hospitalized.

Acknowledgement

We acknowledge the central contributions made by the following members of our multidisciplinary team that provided the coordination and integration of efforts in treating this family: Dr. Elisabeth Perl, Child Psychiatry; Dr. Harshavardhan and Dr. Young Shin, Adult Psychiatry; Mrs. Lorraine Levy and Mrs. Naomi Weiner, Social Service; Ms. Bonnie Padrusch and Ms. Rita Hecht, Psychology Division; Ms. Carolyn Cross, Activity Therapy; and the nursing staff that worked with the family.

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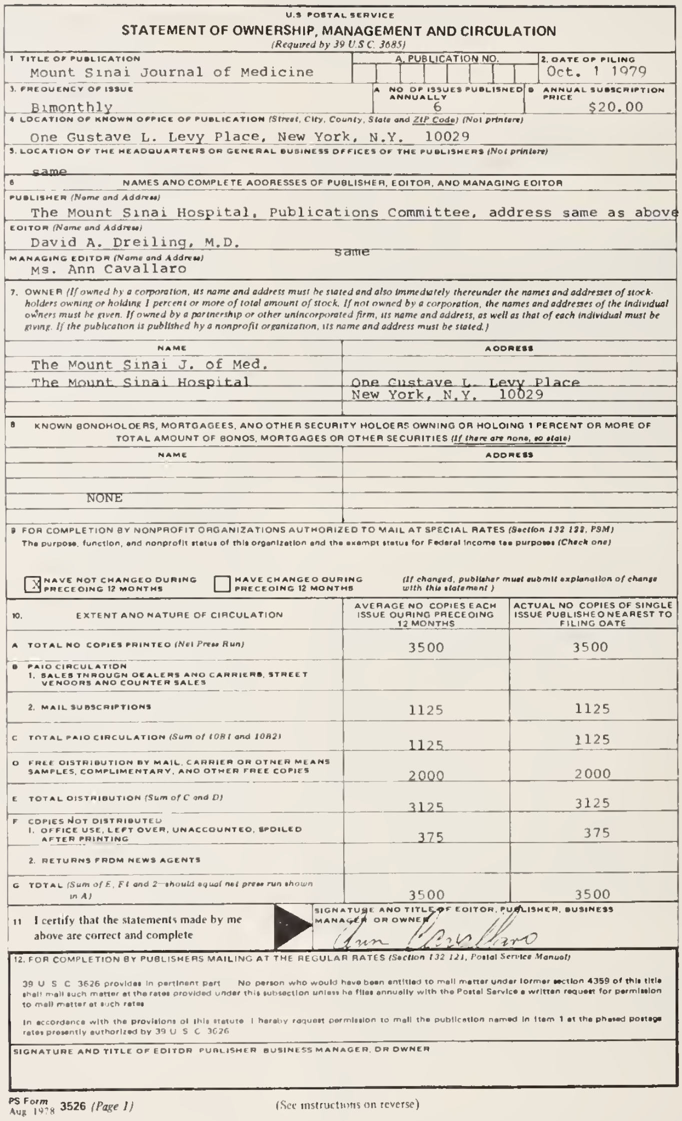

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Research and Development

Vincent P. Dole, M.D.

The theme is discovery. Creative minds have always been rare, but for better or worse their insights have shaped history. Indeed, we can date the beginning of the human species from the time that a few innovative creatures discovered new uses for stones and fig leaves. The stones led to tools and then to science; the fig leaves gave us religion. Considering the problems that have followed, one might regret these discoveries, but it is too late to go back. Anyway, the species has managed to survive and fill the earth. So far, each generation has found ways to deal with the problems it inherited, while producing new discoveries and new problems for its descendents. Whether or not our luck will hold is not entirely clear.

The population of the world continues to rise exponentially, with staggering projections for doubling and redoubling in the next century. No obvious ways can be seen to escape depletion of resources, serious pollution of the environment, shortages of food, fresh water and energy. Perhaps these fears are exaggerated. The public might be right in assuming that these technical problems can be solved with new discoveries, but the future is not assured. All that can be said at this time is that the problems of the immediate future are too serious for pessimism.

Medical science must be seen in this broad perspective. Diseases result from interactions between humans and their environment, which can change faster than they can adapt. Starvation, environmental toxins, psychological stresses demand major adjustments. Sometimes survival is possible only in a crippled state. To understand the complex interactions between stress and physiologic resistance, which we call disease, diverse facts must be assembled. Many of the pieces of these puzzles already exist in technical reports. The difficulty lies in seeing the relevance of technical detail to the cure of a chronic disease when the phenomenon has appeared in another context.

The conventional response to a problem such as this is a call for more money. I disagree. The limiting factors in medical discovery today seem more structural than financial. Medical research may already be over-funded. Further increases in expenditures under present conditions of funding could reduce the prospects for integrative thought while increasing the flow of trivia. If this seems hard to believe, read the abstracts of the big, expensive, national scientific meetings. Look critically at the long bibliographies of persons who are rated as "productive." How much of this work can be honestly rated as discovery, and how much is small, derivative busywork that is required by the system? How else can ambitious scientists obtain grants to fund their laboratories? How can they support a large staff and buy expensive equipment? How can they achieve professional status, win election to societies and be rewarded with tenure? Could their institutions survive without the overhead income provided by their grants? To put the issue bluntly, medical science has become big business. Infusing more money would expand the establishment, but it would not necessarily make it more effective in solving the major problems of society. At its worst, the present system of financing research diverts creative talent to busywork.

Pursuing this thought, let us see what we need. A discovery may be defined as an unexpected finding with large consequences; a development, conversely, is a predictable finding with limited outcome. Penicillin and the identification of DNA as the transforming factor on pneumococci were discoveries; a host of antibiotics and an enormous number of papers on molecular biology developed these observations. Much of the derivative work has been of great value–the importance of a discovery is measured by the impact of subsequent developments–but the point to be made here is that a discovery, like an ore vein, is a limited resource. Continued mining around the original shaft leads to lower yields at increasing expense. Discovery is the limiting factor in medical advance. How can we encourage it?

Unfortunately, the university-goverment complex utilizes its talent for more immediate needs. When an investigator shows imagination in research and has demonstrated his ability to obtain grants, he becomes a grant writing professor. If he proves to be a good administrator, he advances to chairman of a department with an in-

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Dr. Dole is Professor and Senior Physician, The Rockefeller University, New York, N.Y.

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creased load of paperwork. The best and the brightest become deans, in which post their main responsibilities are balancing the institutional budget and resisting the demands of the faculty. Discoveries, if they appear in this system, are incidental to the serious work of paying the bills.

Nor is the government more sympathetic to discovery. Funding agencies, sensitive to political pressure, require elaborate applications in which each proposal is justified by assurance of success. Traces of wonder or uncertainty must be expunged to pass the review committees, that are largely composed of experienced grant writers. The most devastating criticism of a proposal is for a reviewer to call it a "fishing expedition." How indeed does one catch fish without fishing; how does one find something unexpected? Ultimately, the massive pyramid of committees and agencies must answer to committees in Congress, that are composed of persons needing to be reelected. Prudence governs at every stage.

The temperament of investigators adds to the problem. More often than not, the creative person is a maverick. His impertinence disturbs the status quo, embarrasses authorities, and threatens the existence of agencies. Bureaucracy does not like the unexpected.

In the past, the need for flexible support has been met by private endowments. Although the quantity of money available for this purpose has always been small in relation to governmental expenditure, it was venture capital and generally effective. Poets and creative scientists bother the establishments, but these essential persons must be kept alive. I am reminded of a story told about Augustus Busch, the beer magnate. Pointing to the research building on his brewery grounds, he is alleged to have remarked: "I always keep a few of those fellows at work. You never can tell when they might stumble into something." Years ago, this remark seemed crude and insensitive. Against the background of bureaucracy, Mr. Busch sounds like Lorenzo de Medici, boldly investing in people.

But can government, which today controls most of the money, stimulate discovery? Can it afford to finance stumblers? The politically safe decisions are time limited fellowships and grants on developmental projects. So far, I can see long-term, risk-taking support is possible only if the risk of failure is distributed in the actuarial sense.

Essentially this means old fashioned institutional authority for funding. At best, the frequency of significant discovery is low. Institutions, unlike governmental agencies and peer review panels, can average their decisions over time and faculty, with the luxury of surviving mistakes because the good results can justify the whole enterprise. Is it too late to restore substantial authority for allocation of research funds to the universities? Or must discovery under governmental support remain a furtive activity of investigators who pay for their fishing by diversion of funds from project grants?

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From Crohn to Crohn's Disease: 1979 An Epidemiologic Study in New York City*

BURTON I. KORELITZ, M.D.

Fifty years have now passed since granulomatous inflammation of the ileum was being encountered and discussed in the laboratories and corridors of The Mount Sinai Hospital of New York by Moschcowitz, Wilensky, Berg, Crohn, Ginzburg and Oppenheimer, preceding the classic publication on Regional Enteritis (1). The terminology—Crohn's disease—has come into common usage by its students throughout the world along with the recognition that the characteristic inflammatory process may involve other segments of the gastrointestinal tract besides the ileum. Over the past ten to twenty years, evidence of a two to fivefold increase in the incidence of Crohn's disease has been reported from the United States (2), Scotland (3), England (4), Sweden (5, 6), Norway (7), and Holland (8). These figures have been derived from patients requiring hospitalization for what proved to be Crohn's disease. With improvement in medical management, fewer patients have required hospitalization. The following is a series of observations on Crohn's disease from the office practice of gastroenterology in New York City, where Crohn also practiced. Changes in incidence, age of onset, sex, ethnic background, familial associations, nature of presentation and extent of involvement are discussed. Additional data are provided, on incidence and extent of involvement, from Mount Sinai where many of the author's observations on the course of inflammatory bowel disease were made over a 25-year span.

While this report represents the practice of one specialist and does not necessarily represent an epidemiologic description of the disease in all countries or even all cities of the United States, it supports many of the changes reported from different parts of the world and may point to the areas that future statistical analyses might explore.

Observations and Discussion

Incidence of Crohn's Disease in Private Practice in New York City

Between 1960 and June 1979, 353 patients with documented Crohn's disease were seen in the author's private office practice in New York City. Not included were patients with an indeterminate type of colitis. Though these patients seen in the office practice environment might have earlier or later been admitted to the hospital, those patients seen only in the hospital situation were excluded.

Figure 1 shows the number of new patients seen each year from 1960 through 1978. The obvious increase in the number of new patients with Crohn's disease need not have any meaning in regard to the annual incidence but, more logically, represents a special interest in the management of inflammatory bowel disease. When data on annual incidence is plotted according to year of onset of disease, however, the bias is significantly modified if not eliminated. Figure 2 shows the number of new cases annually according to the year of onset, independent of the year first seen in private practice, and demonstrates the dramatic increase in the number of cases of Crohn's disease from the early 1950s through the mid-1970s. Whereas, there was a twofold increase from the 1930s and 1940s to the 1950s, there was a fivefold increase from the 1950s to the 1960s. Table I shows the mean number of new cases per year according to decade and suggests a twenty-one fold increase over a 40-year period from 1935 to 1974. This data, however, is exaggerated when it is recognized that the majority of patients were seen for the first time within five years of onset of symptoms (Fig. 3). Since the patients in this study were first seen in 1960, patients with onset prior to 1955 are less likely to be

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* Presented at a workshop in Cape Town, South Africa, August, 1979.

From the Division of Gastroenterology, Lenox Hill Hospital, New York, N.Y.

Requests for reprints should be sent to Dr. B. Korelitz, Lenox Hill Hospital, 100 E. 77th St., New York, N. Y. 10021.

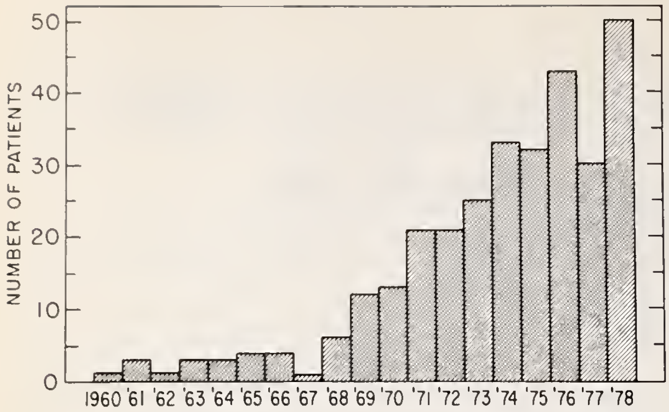

FIG. 1. Incidence of Crohn's disease in private practice, New York City (1960–1978), based on new patients/year.

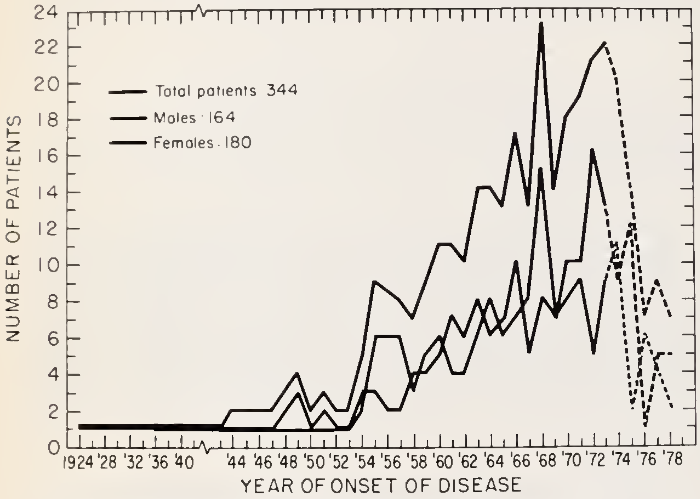

FIG. 2. Incidence of Crohn's disease in private practice, New York City (1960–1978), based on year of onset of disease.

represented in the study. Despite this shortcoming, the documented trend clearly supports the conclusions based on data from the United States, the United Kingdom and Scandinavia on the increasing incidence of Crohn's disease.

Incidence of Crohn's Disease Compared with Ulcerative Colitis

During the 19-year period from 1960–1978, 321 patients with Crohn's disease were seen in private practice compared with 302 patients with ulcerative colitis (Table II). The total number of patients with ulcerative proctitis and indeterminate colitis are noted as well.

In the past, when the cumulative incidence of Crohn's disease was compared with ulcerative colitis, the latter had been considered more common—in a ratio of 2:1 or even 3:1. As a result of the increasing incidence of new cases of Crohn's disease, this is no longer the fact. Crohn's disease is now seen more commonly in private practice than ulcerative colitis. If cases of ulcerative proctitis are combined with ulcerative colitis, the total remains larger than that for Crohn's disease but the difference is not as large as reported in older studies.

Sex Distribution

Figure 2 also shows the sex distribution of patients with Crohn's disease according to year of onset. In most years, there were more females than males. In the early studies by Crohn, ileitis and right-sided colitis were more common in males than females (9). In this study, the reverse has been found. In Table II, the sex distribution in Crohn's disease is compared with ulcerative colitis and ulcerative proctitis. Ulcerative proctitis was also more

TABLE I

Mean Number of New Cases/Year by Decades

According to Year of Onset

1935-1944	0.8/yr.
1945-1954	2.0/yr.
1955-1964	9.5/yr.
1965-1974	18.0/yr.

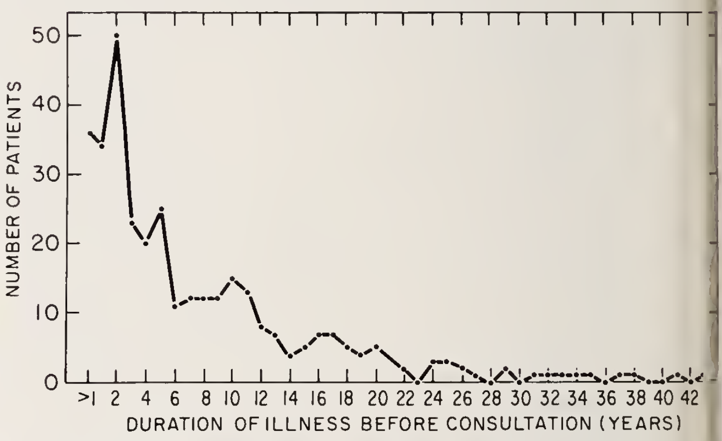

FIG. 3. Crohn's disease. Time from onset of symptoms until seen in consultation.

TABLE II

DIAGNOSTIC DISTRIBUTION OF IBD
NEW YORK CITY (1960 - 1978)

	TOTAL:	MALE	FEMALE
Ulcerative colitis	302	155	147
Ulcerative proctitis	94	41	53
Crohn's disease	321	147	174*
Indeterminate	32	13	19

*57% were female

common in females but ulcerative colitis occurred more frequently in males.

Ethnic Distribution

Table III illustrates the ethnic distribution of the different forms of inflammatory bowel disease and Table IV notes the sex distribution of Jews and Gentiles in each of the most prevalent groups, so that comparisons can be made between Crohn's disease and ulcerative colitis. Crohn's disease has been considered an entity that prevails among Jews much more commonly than among Gentiles (10) and far more frequently in whites than in blacks. Crohn anticipated that evidence would someday disprove this (9). The early reports of ileitis and ileocolitis came from Jewish hospitals and other large institutions in Eastern seaboard cities and in Chicago where the percentage of Jews in the population was very high. Therefore, it would be expected that the ratio of Jews to Gentiles with most diseases would be high in these areas. An exception is taken from a report on Crohn's disease in American veterans occurring predominantly in Jews (11). In this study the disease, as expected, occurred mostly in Jews (7). Similarly, ulcerative colitis and ulcerative proctitis were seen mostly in Jews. Notable among other ethnic groups were the large numbers of Italian and Irish patients both with Crohn's disease and ulcerative colitis. These figures are most likely in proportion to the percentage of these ethnic groups in the local population. Cases of both forms of inflammatory bowel disease remain infrequent among blacks.

Analysis of sex distribution among Jews and Gentiles has been revealing (Table IV). Though Crohn's disease occurs more often in females, the sex distribution among Jews with Crohn's disease was equal, contrasting with 65% of Crohn's disease in Gentiles occurring in females. The female preponderance in Crohn's disease, therefore, is accounted for in the increase of the disease among non-Jewish females. In patients with ulcerative proctitis, which also occurs more commonly in females, there were four times as many Jewish females with the disease as there were Gentile females. Gentile males suffered with ulcerative colitis (59%) more often than Gentile females.

Despite the special situation of high ratio of females among the Gentile patients in New York with Crohn's disease, the increasing incidence has been shared by Jew and Gentile (Fig. 4) and remains in proportion to the ethnic distribution in the New York population. This conclusion is supported by data from another large city in the United States (Houston, Texas) where the Jewish population is much smaller and the percentage of Jews with Crohn's disease is proportionately smaller (Fig. 5).

TABLE III

ETHNIC DISTRIBUTION OF IBD
NEW YORK CITY (1960 - 1978)

	JEWISH	GENTILE:	Italian	Irish	Black
Ulcerative colitis	224 (74%)	78	25	10	2
Ulcerative proctitis	73 (74%)	25	8	3	2
Crohn's disease	230 (71%)	91	23	10	4
Indeterminate	17	13	3	2	0
	544	207			

TABLE IV

ETHNIC AND SEX DISTRIBUTION OF IBD
NEW YORK CITY (1960 - 1978)

		JEWISH	GENTILE
Ulcerative colitis	male	111	46
	female	113	32
Ulcerative proctitis	male	27	15
	female	$\boxed{42}$	10
Crohn's disease	male	116*	31
	female	114*	$\boxed{57^{**}}$

*Equal numbers of Jewish males and females
**65% of Gentiles were female

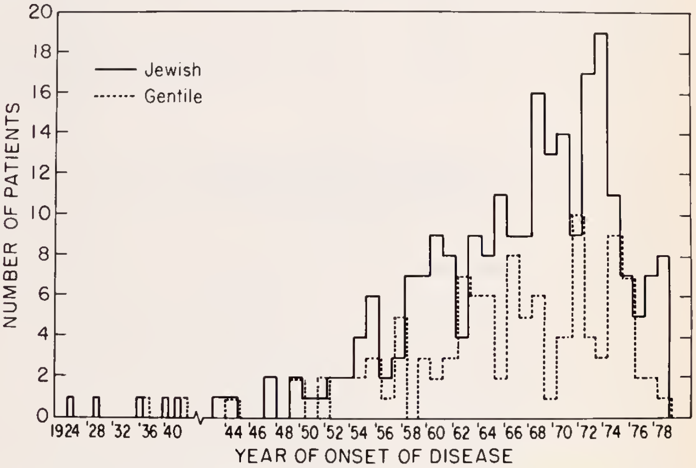

FIG. 4. Crohn's disease in private practice, New York City (1960–1978), ethnic background.

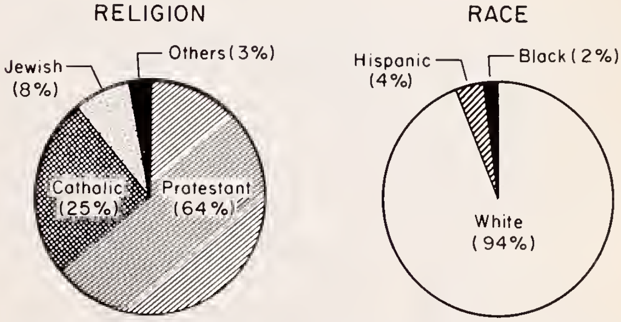

FIG. 5. Religious background and race in 261 patients with IBD seen at Kelsey Seybold Clinic, Houston, Texas. (Data courtesy of Philip S. Bentlif, M.D.)

Age of Onset

The age of onset of Crohn's disease in five arbitrarily divided groups is shown in Table V.

It has been recognized since its first published description that Crohn's disease is a disease of young people. Crohn found that the onset was most common in the 20–30 year old age group. In the current study, the trend is toward a still younger age of onset with most cases recognized between ages 16 and 21. Eighty-two percent of the patients studied had their initial symptoms before age 31, and 56% before age 22. When two periods of time are compared (Table VI) it is clear that the increase in incidence of the disease is accounted for by an increased number of patients with onset during the most common age period of onset—16–21.

TABLE V

CROHN'S DISEASE IN PRIVATE PRACTICE
NEW YORK CITY (1924 - 1979)
Age of Onset

AGE RANGE	NO. OF PATIENTS		
4 - 10	24	(7%)	56%
11 - 15	68	(20%)	
16 - 21	101	(29%)	
22 - 30	89	(26%)	
31 - 49	42	(12%)	
50 - 65	19	(6%)	
	343		

TABLE VI

CROHN'S DISEASE IN PRIVATE PRACTICE
NEW YORK CITY
Comparison of Age of Onset in Two Different Periods

AGE RANGE	1949 - 1964		1972 - 1978	
4 - 10	8	(6.6%)	6	(6.2%)
11 - 15	23	(19.1%)	19	(19.6%)
16 - 21	32	(26.6%)	31	(32.0%)
22 - 30	32	(26.6%)	27	(27.8%)
31 - 49	14	(11.6%)	10	(10.3%)
50 - 65	11	(9.1%)	4	(4.1%)
	120		97	

Genetic Inferences

Support for a genetic predisposition to Crohn's disease is provided by a 20% occurrence of one or more blood relatives also suffering from Crohn's disease or, less often, from ulcerative colitis.

The relationships are listed in Tables VII and VIII. The discrepancy in totals is accounted for by more than one member of a family being a patient. When the name of the relative's disease was disclosed by the patient as ulcerative colitis but not necessarily documented, it was listed as Crohn's v. ulcerative colitis; whereas, possible Crohn's meant suggestive symptomatology without verification of any inflammatory bowel disease.

TABLE VII

FAMILY RELATIONSHIPS IN
72 PATIENTS WITH CROHN'S DISEASE

	CROHN'S	CROHN'S VS ULCERATIVE COLITIS	POSSIBLE CROHN'S
Father - Daughter	13	3	1
Father - Son*	8	3	1
Mother - Daughter	5	2	2
Mother - Son*	3	3	
Brother - Sister	14	1	
Brother - Brother	6	2	
Sister - Sister	4	2	
Grandparents - Grandchild*	3	1	1

*3 generations of Crohn's disease in 2 families.

TABLE VIII

FAMILY RELATIONSHIPS IN
72 PATIENTS WITH CROHN'S DISEASE
(cont.)

	CROHN'S	CROHN'S VS ULCERATIVE COLITIS
First cousin	14	6
Second cousin	2	1
Paternal aunt	7	3
Paternal uncle	6	2
Maternal aunt	-	4
Maternal uncle	3	2
	88	35

Table IX shows the number of family relationships for each patient with Crohn's disease who had one or more relatives with the same disease. The most common types of family relationships suggest a polygenic type of inheritance (12), those at greatest risk being those who share the most genes with the patient. Patients with Crohn's disease have many relatives with ulcerative colitis as well as Crohn's disease, and patients with ulcerative colitis have many relatives with ulcerative colitis but few with Crohn's disease (10). It may be postulated that Crohn's disease results from a larger concentration or summation of genes and ulcerative colitis from a lesser.

Familial Crohn's disease and ulcerative colitis occur most commonly among Jews in whom inbreeding is prevalent. Nevertheless, the 56 family relationships included 14 (19.4%) gentile families. In eight of these 14, the relatives of the parent probably had ulcerative colitis rather than Crohn's disease; while in 25 of 42 Jewish families, the relative was more likely to have Crohn's disease. The two families with three generations of Crohn's disease were both Jewish, and five patients belonged to one family with eight members suffering with Crohn's disease, including a father with four children, his

TABLE IX

Number of Family Relationships in 353 Patients with Crohn's Disease

No. Relatives	No. Families
0	281
2	36
3	15
4	3
8	1

sister, his brother and his brother's son. Two patients had twin siblings, neither of whom had any indication of the disease.

Table X shows other relationships of interest among the Crohn's disease patients. These include a woman whose husband developed the disease after they were married, but this is rare. (Subsequently, the older of two sons has also developed Crohn's disease.) The infrequent occurrence of such cases provides evidence against exposure to a common organism as an etiologic factor in contrast with genetic predisposition. In the other instance of inflammatory bowel disease in husband and wife, one had Crohn's and the other ulcerative colitis; they were married after the onset of disease.

The incidence of carcinoma of the colon occurring in parents of patients with Crohn's disease is remarkably high and raises consideration of increased risk of malignancy in bowel involved with Crohn's disease.

Nature of Presentation

The symptoms of Crohn's disease that best correlate with the distribution of the disease has been reported previously (13). These symptoms, however, do not necessarily correspond to the symptoms at the time of onset of the disease. A review of records for earliest symptoms in the 353 patients seen in private practice revealed that, in most cases, there were two symptoms occurring simultaneously that heralded the onset of disease. In fewer cases, one symptom distinctly preceded the other; and in still fewer cases three symptoms occurred together so that it could not be determined that one of the three preceded another. Accordingly, for purposes of analysis, one, two, or three symptoms were considered as the nature of presentation.

The most common modes of presentation of Crohn's disease, in order of frequency, were diarrhea, abdominal pain or cramps, fever, perirectal abscess, blood in the stool, or possible appendicitis leading to exploration. The number of instances of each according to age range at time of onset are shown in Table XI.

TABLE X

OTHER FAMILY RELATIONSHIPS IN PATIENTS WITH CROHN'S DISEASE

Husband and wife with IBD	2	
Mother with carcinoma of colon	4	3.4%
Father with carcinoma of colon	4	
Mother with carcinoma of small bowel	1	
Father with Hodgkin's disease	1	
Brother with Hodgkin's disease	1	

When an analysis of mode of introduction was made according to age of onset, a few interesting associations were found. In the group with onset of symptoms between ages four and ten, diarrhea, abdominal pain or cramps and fever were the most common symptoms at onset similar to other groups with onset before age twenty-two, but the incidence of blood in the stool as a first symptom was particularly high. Similarly, introduction of Crohn's disease with a perirectal abscess or with a clinical picture suggesting appendicitis was notably high in the 22–30 age group and both perirectal abscess and blood in the stool were high in the 31–49 age group.

Other modes of presentation, still occurring with some frequency, are listed in Table XII according to age group, and all remaining initial symptoms are noted in Tables XIII and XIV. Figure 6 lists the six most common methods of presentation according to year of onset of disease.

Though infrequent, appearance of the disease with fistulae or hypertrophied anal skin tabs should lead to quick diagnosis. Personality changes, retarded growth and development, mouth or lip lesions, and iritis or pus in the lumen of the rectum on sigmoidoscopy should all arouse suspicion of Crohn's disease.

Initial Extent of Involvement by X-Ray Examination

In each of 345 cases, the initial extent of Crohn's disease was determined and grouped into ileitis (disease

TABLE XI

NATURE OF PRESENTATION OF CROHN'S DISEASE
According to Age

PRESENTATION	AGE RANGE						TOTAL
	4-10	11-15	16-21	22-30	31-49	50-75	
Diarrhea	13	33	63	46	23	10	188
Pain or cramps	8	28	42	40	6	8	132
Fever	5	8	13	6	3	-	35
Peri-rectal abscess	1	7	6	$\boxed{9}$	$\boxed{6}$	-	29
Blood in stool	$\boxed{4}$	7	5	6	$\boxed{6}$	-	28
? Appendicitis	0	3	5	$\boxed{11}$	1	2	22

TABLE XII

NATURE OF PRESENTATION OF CROHN'S DISEASE
According to Age
(cont.)

PRESENTATION	AGE RANGE						TOTAL
	4-10	11-15	16-21	22-30	31-49	50-75	
Weight loss	3	8	13	0	1	-	36
Nausea or vomiting	1	1	3	3	2	1	11
Joint pains, muscle aches	-	3	4	2	-	-	9
Erythema nodosum	-	2	-	2	-	-	4
Mouth lesions	2	1	-	1	-	-	-

TABLE XIII

CROHN'S DISEASE
Less Frequent Presentations

Retarded growth	4
Ileo-vesicle fistula	3
Bloating	3
Lower GI bleeding	2
Fatigue	2
Anorexia or malaise	2
Personality changes	2
Skin lesions	2
Lip lesions	2

TABLE XIV

CROHN'S DISEASE
Less Frequent Presentations
(cont.)

Dyspareunia	1
Pus/rectum	1
Chills	1
Obstruction	1
Explored for PID	1
Explored for valvulus	1
Perforations	1
Constipation	1
Alternate diarrhea plus constipation	1
RLQ mass	1
Multiple perineal sinuses	1
Fistula at appendectomy site	1
Labial fistula	1
Anal skin tags	1
Iritis	1
Backache	1
Ankle swelling	1

apparently limited to the ileum), ileocolitis (combination of ileum and colon), colitis (limited to colon–right side or almost total), left-sided colitis (colitis limited to the left colon) and extensive (long segment of small bowel with

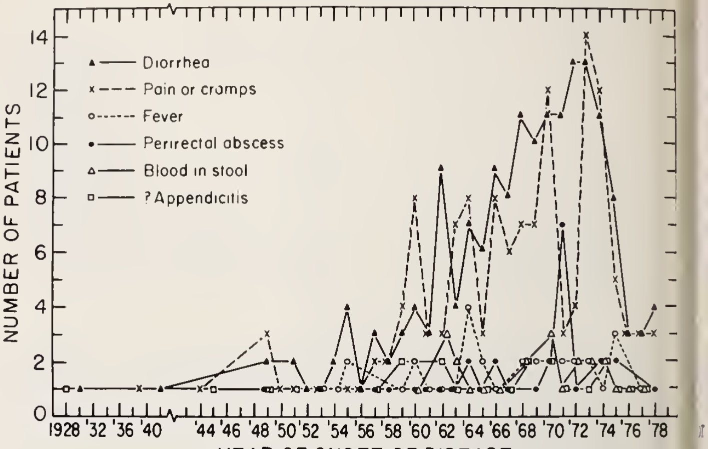

FIG. 6. Crohn's Disease. Nature of presentation according to year of onset.

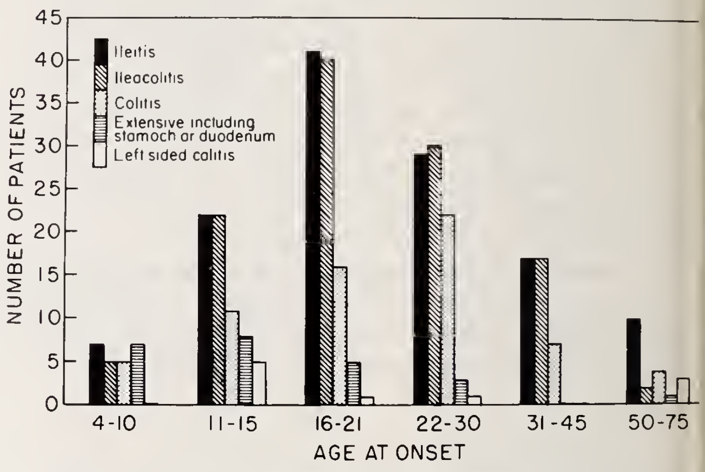

FIG. 7. Extent of involvement in Crohn's disease according to age of onset.

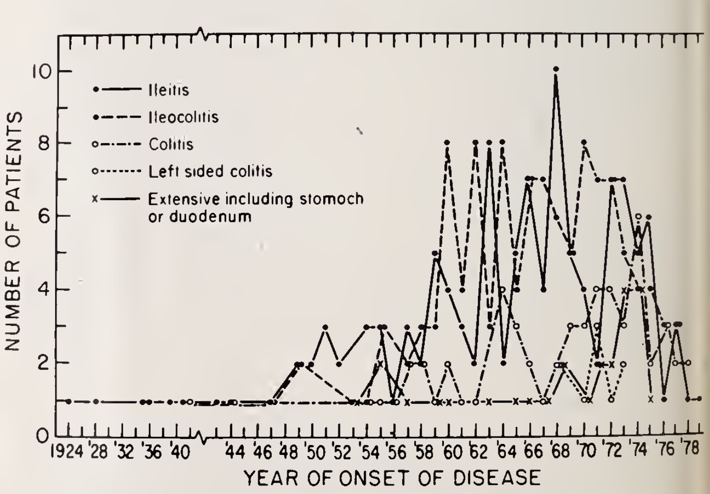

FIG. 8. Extent of involvement in Crohn's disease according to year of onset.

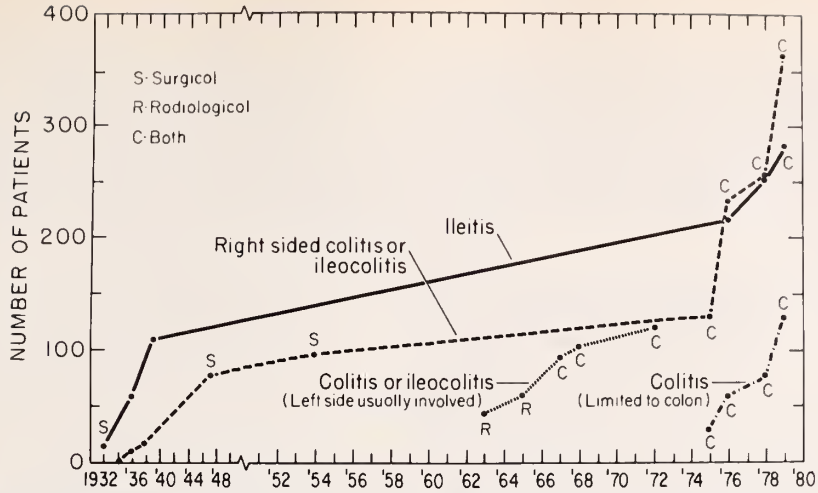

Fig. 9. Incidence of Crohn's disease at The Mount Sinai Hospital. (Recent data, courtesy of Adrian J. Greenstein, M.D.)

or without colon and usually involving stomach, duodenum or both). These five distribution groups are shown in Figure 7, according to age range at time of onset. Not included are two cases of Crohn's disease limited to the anus (anal Crohn's) and one case of each, limited to the rectum and the appendix. Similarly, Figure 8 shows the frequency of the five most common distributions of gross disease according to year of onset of disease.

Ileitis remains the most common distribution or extent of involvement as determined by x-rays of Crohn's disease. When determined for all age at onset groups in recent years, however, ileocolitis has been more common than ileitis in those ages 22–30. When the ileocolitis and colitis groups are combined, Crohn's disease with colonic involvement becomes the most common distribution. The number of cases with those limited to the colon and those with duodenal or gastric involvement has also increased in recent years and indications of Crohn's duodenitis have become quite common.

Figure 9 illustrates the incidence of Crohn's disease at The Mount Sinai Hospital of New York, based on reports from the original 1932 publication on regional ileitis until the present (1, 14–27). The available information was divided into cases of ileitis, ileocolitis with different extents of colonic involvement, and colitis as specifically identified or estimated from each publication. In the early years, all distributions of the disease were determined by surgical specimen; in later years, the common denominator was the x-ray diagnosis and, most recently, data on extent of involvement has been determined by combinations of sigmoidoscopic findings, x-ray features and surgical specimens.

The experience at Mount Sinai Hospital supports the rapid increase in incidence of ileocolitis and colitis during the past decade. In 1932, all 14 patients had ileitis (1), but soon thereafter Colp reported a case with simultaneous involvement of terminal ileum and cecum (14). The reports of right-sided colitis and ilecolitis (15–26) followed. Allowing for lack of recognition of colonic involvement in the early years, and the narrowed terminal ileum still being the most prominent segment of disease even when colitis is present, the increasing documentation of colonic involvement with Crohn's disease in both the office and the hospital situation is convincing and most likely represents a real change in distribution of the disease. This is explained, in part, by recognizing that perhaps as many as half the cases of inflammatory bowel disease involving the colon were pathologically Crohn's disease. It is also, however, related to Crohn's disease being a diffuse process with lesions occurring in both mouth and anus, and is supported by finding granulomas and other microscopic lesions in 20%–45% of biopsies of normal appearing duodenal (28) and rectal (29) mucosa with overt involvement elsewhere.

Conclusions

As determined by analysis of 353 patients with Crohn's disease seen in the author's private office practice of gastroenterology in New York City during the last 20 years:

1) The annual incidence of Crohn's disease has increased markedly over the past 40 years.
2) Crohn's disease is now seen more often in private practice than ulcerative colitis.
3) Crohn's disease occurs more commonly in females (57%) than in males. The female preponderance is accounted for by the high percentage of cases in non-Jewish females (65%) in comparison with males (35%), since the sex distribution in Jews is equal.
4) Crohn's disease in New York City occurs mostly in Jews (71%). This is explained in part by the large percentage of Jews in the population of New York City. In other regions of the country where the proportion of Jews is small, the percentage of pa-

tients with Crohn's disease being Jewish is also small.

5) The most common age range with onset of symptoms in Crohn's disease is 16 to 21, a younger range than was known 40 years ago, so that 82% had initial symptoms before the age of 31. The increasing incidence is accounted for by new patients in the 16–21 age group.
6) Support for a genetic predisposition in the form of a polygenic type of inheritance is derived from a) 20% occurrence of Crohn's disease or ulcerative colitis in blood relatives; b) most instances of two or more members of a family with Crohn's disease occurring in Jewish families; c) two families with three generations of patients with Crohn's disease being Jewish; and d) one family with eight members suffering with Crohn's disease also being Jewish.
7) Diarrhea, abdominal pain, cramps, and fever are the most common modes of presentation of Crohn's disease. Blood in the stool is a significantly common form of onset in the four to ten and 31 to 49 age groups. Perirectal abscess is a significantly common introduction in the 22 to 49 age group and a clinical picture suggesting appendicitis in the 22–30 age group.
8) While Crohn's disease limited, by x-ray distribution, to the terminal ileum remains common, ileocolitis has occurred more often in recent years than ileitis. Cases with disease limited to the colon and cases with involvement of the stomach or duodenum are increasing in frequency.
9) At Mount Sinai, where regional ileitis was first reported, the incidence of inpatients with Crohn's disease has also increased and cases of ileocolitis and colitis have recently increased faster than ileitis as has been reported in this study.

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Multiple Antibiotic Resistant *Salmonella Agona* Infection in Malnourished Neonatal Twins

JOHN G. LARSEN, M.D., BRUCE A. HANNA, PH.D., EDWARD J. BOTTONE, PH.D., WARREN H. KURTZ, PH.D., LEONARD KASEN, M.D., and STANLEY C. URETSKY, M.D.

Abstract

A pair of neonatal twins were evaluated with different clinical manifestations of infection caused by a multiple antibiotic resistant *Salmonella agona*. Resistance was shown to be mediated by several plasmids. The twins showed differences in both immunologic characteristics and host response. Factors responsible for the differences in host response and clinical manifestations are discussed.

Introduction

Despite advances in epidemiology and antimicrobial therapy, salmonellosis continues to be a major cause of morbidity and mortality, especially in infants and the elderly. We describe identical male twins who had different clinical infections caused by a multiple antibiotic resistant *Salmonella agona*. The twins also had disparate immunologic characteristics and responses. Twin B, who developed septicemia, failed to develop antibodies to *S. agona* lipopolysaccharide (O-antigen), and had a delayed antibody response to oral polio vaccination. Twin A, who had uncomplicated *S. agona* gastroenteritis, developed antibodies to the infecting strain and had a normal immunologic response to oral polio vaccination.

The isolate was unusual because of its antimicrobial susceptibility pattern, that revealed resistance to most commonly used chemotherapeutic agents including ampicillin, chloramphenicol, and gentamicin. This strain was also shown to harbor extrachromosomal elements capable of transmitting the resistance phenotype of *Escherichia coli.*

Case Report

The twins were born in Colombia, South America, following a full term, uncomplicated, pregnancy, labor, and delivery. At birth, twin A weighed 2180 g and twin B weighed 2060 g. At three days of age, the twins were transferred to an orphanage where they contracted pneumonia and were treated with parenteral penicillin and kanamycin. Following this occurrence, the twins were adopted by a New York City couple and brought to the United States. Upon arrival here at age one month, the twins were examined and appeared to be chronically malnourished, although in no acute distress. At this time, twin A weighed 2268 g and twin B weighed 1928 g. Three days prior to admission, twin B developed cough and coryza and one day prior to admission, he developed greenish, diarrheal stools, without blood or mucus. The following day, the infant developed respiratory distress and was admitted to The Mount Sinai Hospital.

Physical examination on admission disclosed an acutely and chronically ill, one month old infant in shock. The temperature was 35°C, pulse 140/minute, respiration 44/minute and labored. The anterior fontanelle and eyeballs were sunken and there was poor skin turgor. There was a pustular erythematous rash in the perineal area. Eyes and ears were normal. Mucous membranes were dry and there was oral thrush. Auscultation of the chest disclosed rales in the right posterior lung field. Cardiac examination was unremarkable. The abdomen was slightly distended, but bowel sounds were present. There was no hepatosplenomegaly. Genitalia and extremities were normal. Neurologic examination disclosed an irritable, alert infant who moved all four extremities equally. Suck was good. Tone and reflexes were normal.

Admission laboratory data on twin B included: Hgb 10.4 g/dl; Hct 30%; WBC 11,500/mm3, 15 Segs, 42 Bands,

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From the Department of Pediatrics and Microbiology, The Mount Sinai Hospital and Mount Sinai School of Medicine, (CUNY), New York, N.Y.

Requests for reprints should be sent to: Stanley C. Uretsky, M.D., Department of Pediatrics, The Mount Sinai Hospital, New York, N.Y. 10029.

35 Lymphs, 1 Monocyte, 3 Metamyelocytes, 2 Myelocytes, and 2 atypical Lymphocytes. Toxic granulation of neutrophils was present, but red blood cell morphology and platelet count were normal. Laboratory values included Na 137 meq/L, K 3.2 meq/L, Cl 117 meq/L, HCO_3 5 meq/L, BUN 17 mg/dl, Glucose 66 mg/dl, Ca 9.2 mg/L, and Mg 2.5 mg/L. Serum osmolality was 282 mosm/L. Lumbar puncture disclosed clear, colorless fluid; cell count revealed only 3 red blood cells. The CSF protein was 29 mg/dl, and CSF glucose was 61 mg/dl. No organisms were observed in Grams' stained smears.

Assay for endotoxin (Limulus test) of the CSF was negative. Urine pH was 5, and blood, ketones, protein, glucose, and cells were absent. Urine limulus test was negative and organisms were not seen on Gram's stain of unspun urine. The stool was green and watery without occult blood. Methylene blue stain showed occasional polymorphonuclear leukocytes. Stool pH was 5 and there were no reducing substances. Chest x-ray showed a right lower lobe infiltrate.

The diagnosis of septic shock was made and the baby was treated with intravenous fluids, salt poor albumin, sodium bicarbonate and packed red blood cell transfusions. Intravenous oxacillin, 200 mg/kg/24h and gentamicin, 7 mg/kg/24h, were begun. Cultures of urine and CSF were sterile and a blood culture drawn prior to administration of antibiotics was negative after 48-hours incubation. The baby's condition improved until the fifth hospital day when he again developed loose stools mixed with bright red blood. Physical examination showed no evidence of anal fissures. Roentgenologic examination of the abdomen was normal. On the following day, a group B *Salmonella* was identified from the patient's admission stool culture as well as from the stool of his brother, twin A, who was suffering from mild gastroenteritis. Oxacillin and gentamicin were discontinued, and ampicillin, 200 mg/kg/24h was begun. The following day, the baby became hypothermic and developed a distended abdomen. Repeat blood, urine, stool, and skin cultures all revealed the presence of a group B *Salmonella*, subsequently identified as *S agona*. The same microbial species was subsequently isolated from the admission blood cultures, drawn prior to administration of antibiotics. Bauer-Kirby antimicrobial susceptibility testing (1) showed that the isolates were resistant to ampicillin, chloramphenicol, tetracycline, tobramycin, kanamycin, and were moderately resistant to cephalothin and gentamicin.

Ampicillin was discontinued and the baby was given cephalothin 150 mg/kg/24h, and gentamicin, 7 mg/kg/24h. As further susceptibility testing showed the organism to be inhibited by trimethoprim-sulfamethoxazole, this drug was added to the regimen. The infant's condition improved, and he began to feed and gain weight. All antimicrobials were discontinued after eight days. Follow up cultures of blood and urine were negative, but the organism persisted in the stool. Repeat susceptibility testing by the two tube broth dilution method (2) revealed that the organism was now resistant to trimethoprim-sulfamethoxazole, cephalothin, and gentamicin, as well as the other antibiotics tested (Table II). Although the organism persisted in the stool, the baby was asymptomatic and was discharged weighing 2550 g.

Presently both twins, now twenty months old, continue to thrive, grow and develop. *S agona* persisted in their stools up to the age of nine months. Twin A, at one year of age, had developed a 1:16 titer against his own *S agona* strain. Twin B, who had developed sepsis, failed to develop antibodies to the *S agona* isolate. Neutralization assay for antipolio antibodies, following three oral vaccinations, demonstrated that twin B lacked detectable antibody until the age of sixteen months, whereas twin A had a measurable titer (1:8–1:32) at age eight months. Both twins had quantitative immunoglobulin and isohemmagglutinin levels within normal limits. (Table I)

Bacteriology

After twenty-four hours incubation on Endo, MacConkey and Hektoen-enteric (H-E) agars, stool cultures from both twins showed many colorless colonies, indicating the presence of a nonlactose fermenting microorganism. On H-E agar, these colonies had black centers, signaling hydrogen sulfide production. For screening purposes, several colonies from both stool cultures were selected and inoculated on Kligler's Iron Agar (KIA) and Christensen's urea agar slants. After 24-hours incubation at 37°C, an alkaline slant and acid butt with extensive hydrogen sulfide was observed in all KIA tubes, while urease activity was absent. Because of these reactions, the isolates were tested serologically and found to agglutinate with both *Salmonella* polyvalent and group B antisera. Following additional biochemical confirmation, both patient isolates were definitively speciated as *S agona* through the courtesy of the New York City Department of Health laboratories.

Concomitant with the stool isolates, blood cultures collected from twin B on the day of admission were noted to contain gram-negative rods subsequently identified as *S agona*. Two tube broth dilution susceptibility studies (2) showed that the stool and blood isolates had identical antibiograms. (Table II) The initial isolates were sensitive to trimethoprim-sulfamethoxazole as determined by the agar disc diffusion technique (1). Minimal inhibitory concentration (MIC) determination disclosed the organism to be resistant to ampicillin 100 ug/ml, cephalothin 50 ug/ml, chloramphenicol 50 ug/ml, gentamicin 50 ug/ml, and tobramycin 50 ug/ml.

To date, no further isolations of either a *Salmonella* or other *Enterobacteriaceae* with similar antibiograms have been observed from human isolates at this hospital.

TABLE I

Antibody Responses and Quantitative Immunoglobulin Levels of Twins A and B

Dates	TWIN A					TWIN B				
	1 mo	6 mos	8 mos	12 mos	16 mos	1 mo	6 mos	8 mos	12 mos	16 mos
DETERMINATIONS										
IgG (mg/dl)	—	—	—	360	—	260	500	—	365	665
IgM (mg/dl)	—	—	—	120	—	50	40	—	35	126
IgA (mg/dl)	—	—	—	17	—	50	24	—	20	50
Salmonella agona O	<1:8	<1:8	<1:8	1:16	—	<1:8	<1:8	<1:8	<1:8	—
Other Salmonella O	neg	neg	neg	GroupE 1:40	—	neg	neg	neg	neg	—
Polio Type I	—	—	1:8	1:32	—	—	—	<1:8	<1:8	1:4
Polio Type II	—	—	1:32	1:32	—	—	—	<1:8	<1:8	1:16
Polio Type III	—	—	1:16	1:32	—	—	—	<1:8	<1:8	1:16
Blood Group A	—	—	—	1:16	—	—	—	—	1:16	—
Blood Group B	—	—	—	1:64	—	—	—	—	1:32	—
Secretory IgA						Not Present				

TABLE II

Antimicrobial Susceptibility Pattern of Salmonella agona Blood and Stool Isolates as Determined by the Two Tube Broth Dilution Method (2).

Antibiotic	Concentration (μg/ml)	Results
Ampicillin	5, 10	Res*
Carbenicillin	25, 100	Res
Cephalothin	7.5, 15	Res
Chloramphenicol	7.5, 15	Res
Colistin	2, 5	Res
Gentamicin	5, 10	Res
Sulfisoxazole	100, 250	Res
Tetracycline	2, 4	Res
Tobramycin	5, 10	Res
Trimethoprim-Sulfamethoxazole	1.25/23.75 Disc Concentration (μg)	Res

* Res = Resistant

Salmonella strains isolated from domestic animals have shown similar resistance patterns (3).

To determine the nature of the observed antibiotic resistance, in vitro conjugation experiments were performed (4). A recombinant deficient *Escherichia coli* mutant, sensitive to all the antibiotics in question, was used as the recipient and the isolated *S agona* as the donor. To allow the bacteria to conjugate, 0.1 ml of individual overnight broth cultures of *E coli* and *S agona* were plated together onto Mueller-Hinton agar. After subsequent 24-hour incubation, a saline suspension of the *E coli–S agona* mixture was prepared from the lawn of the two organisms. To recover the *E coli*, 0.1 ml of this suspension was plated on a minimal agar medium that contained lactose as the sole carbon source, thus preventing the growth of *S agona*, which is unable to metabolize this substrate. Following overnight incubation, several colonies were picked, biochemically confirmed as *E coli*, and tested for antibiotic susceptibility. As a result of conjugation, the *E coli* isolates acquired a resistance pattern identical to that of the *S agona* with exception of the colymycin resistance marker. The recombinant *E coli* remained susceptible to colymycin but acquired resistance to ampicillin, carbenicillin, cephalothin, chloramphenicol, gentamicin, kanamycin, sulfisoxazole, tetracycline, and tobramycin. Barring plasmid exclusion, it seems probable that colymycin resistance was coded for by a gene on the chromosome, while the eight other markers were coded for by genes residing on one or more extrachromosomal plasmids or resistance transfer factors (RTF). It seems improbable that the codes for all transferable markers were on a single plasmid, since *S. agona* isolates from 6 and 9 month follow-up stool cultures carried various complements of markers (Table III). While antibiogram profiles of subsequent isolates varied from multiply resistant to predominantly susceptible, in no instance was colymycin resistance lost.

Discussion

According to the Kaufmann-White schema, *S agona* is placed with strains possessing group B antigenic determinants (5). As a specific strain, it has been prevalent in South America, but was not considered of great importance until the early 1970's when outbreaks of gastroenteritis caused by this organism were reported from Italy, England, and the United States (6–8). Epidemiologic studies of the American outbreak indicated acquisition through ingestion of meat from animals who had been fed fish meal imported from Peru. Further examination of these products revealed contamination with *S agona* in numerous instances. Since 1971, gastroenteritis caused by *S agona* had been reported with increasing frequency and in 1976, *S. agona* ranked third among the ten most frequently reported serotypes from human sources (9). The disease reported in all of these outbreaks has been gastroenteritis without systemic infection. *S agona* rarely is associated with invasion of the blood stream or with other systemic foci of infection. However, the facility with which this organism is transmitted in epidemics,

TABLE III

Results of Mating Multiple Antibiotic Resistant S. Agona Isolate with Recipient Antibiotic Susceptible E Coli

Antibiotic	S *Agona* Stool	*E Coli* Recipient	Recombinant *E Coli*	Representative of *S Agona* Isolates Antibiograms from 6 and 9 month follow-up stool Culture		
				#1	#2	#3
Ampicillin	R	S	R	R	R	S
Carbenicillin	R	S	R	R	R	S
Cephalothin	R	S	R	R	S	S
Chloramphenicol	R	S	R	R	R	S
Gentamicin	R	S	R	R	S	S
Kanamycin	R	S	R	R	S	S
Sulfisoxazole	R	S	R	—*	—*	—*
Tetracycline	R	S	R	R	R	S
Tobramycin	R	S	R	R	S	S
Colymycin	R	S	S	R	R	R

* Not tested

and the dramatic increase in its prevalence has led to speculation that *S agona* may have acquired enhanced virulence (9).

Multiple antibiotic resistance has increased steadily over the past several years, both in *Salmonella* species and other *Enterobacteriacea* (3, 10). This resistance is primarily plasmid mediated (10). A recent survey of antimicrobial resistance in *Salmonella* isolated in Ontario, Canada revealed 12.4% of human and 38.2% of animal strains resistant to both chloramphenicol and ampicillin. All of these strains however, were sensitive to gentamicin (11). The *S agona* isolated from our patients was distinguished by its resistance to gentamicin as well as chloramphenicol, ampicillin, and other commonly used antibiotics. During the course of antimicrobial therapy, the organism acquired resistance to trimethoprim-sulfamethoxazole, the only agent to which the organism was initially sensitive. Although it was demonstrated that antimicrobial resistance was plasmid mediated, to date we have not found microbiologic evidence to suggest that these plasmids has been transferred to other bacterial species in our patient population.

The pattern of *Salmonella* infection in a given host depends upon the infecting species, the number of organisms ingested, and host susceptibility (12). Since *S agona* is not a species commonly associated with bloodstream invasion, host factors must have been primarily responsible for the different manifestations of infection in these twins.

Salmonella survive and multiply within macrophages (13). Activated macrophages, in conjunction with antibody, appear to be the major defense against *Salmonella* invasion (14). Studies of neonatal macrophage function have shown that their macrophages have an impaired chemotactic response, although intracellular killing of organisms is normal (15, 16). Such faulty chemotaxis may increase neonatal susceptibility to *Salmonella* invasion. Furthermore, neonates have low levels of serum IgM, the antibody chiefly involved in protection against gram negative bacteria (17). Secretory IgA may also be important in host resistance against *Salmonella*. Antibodies against *Salmonella* have been found in the colostrum of women who have had *Salmonella* gastroenteritis during pregnancy (18). Our patients were not breast fed and had no detectable secretory IgA at the time of the initial hospitalization. Malnutrition, which increases host susceptibility to a variety of infections, may have served as another predisposing factor in these twins. Additionally, it has been shown that broad spectrum antibiotics increase host susceptibility to *Salmonella* infection (19) and our patients were treated with such agents prior to clinical manifestations of their *Salmonella* infection.

The poor antibody response on the part of twin B to the O-antigen of *S agona* is also noteworthy. The antibody response to *Salmonella* O-antigen is variable. Thirty-four percent of patients with untreated typhoid fever do not develop a significant "O" titer (20) and patients who are carriers or have gastroenteritis are even less likely to develop titers (21). While Smith showed that newborns immunized with killed typhoid vaccine develop H but no O-antibodies (22), Hodes et al showed that newborns are capable of responding to *Salmonella* st paul bacteremia with antibody directed against somatic antigens (23). Another explanation for the lack of antibody response could be an immune deficiency. However, our patients have thrived since their recovery and have not had frequent infections. Furthermore, their levels of immunoglobulins and isohemagglutinins have been normal and they have tolerated their series of live immunizations without complications.

Two different clinical syndromes developed in identical twins who were infected with the same organism. One explanation for this occurrence could be that twin B ingested a greater number of organisms, thereby increasing the chance of invasion. A second explanation is that twin B had decreased resistance to infection relative to his twin brother. In support of this contention, twin B unlike his brother, failed to develop antibodies to *S. agona*. Furthermore, twin A had a normal response to oral polio vaccination, whereas twin B failed to develop measurable antipolio antibody until sixteen months of age. We speculate that twin B's greater degree of malnutrition may have interfered with his antibody response. This is supported by a study that demonstrated a poor antibody response to typhoid vaccine in children with Kwashiorkor (24). Furthermore, as twin B regained adequate nutrition, he developed antibodies to oral polio vaccine.

These patients are a notable demonstration of how host factors (including age, nutritional status, and immunologic capability), environmental factors (including antibiotic therapy and contamination of the environment), and characteristics of the organism (including virulence and antimicrobial resistance) interact to produce a specific pattern of infection in a given host.

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Xiphodynia-Another Cause of Atypical Chest Pain: Six Case Reports

HERSCHEL J. SKLAROFF, M.D., F.A.C.P.

Abstract

Six cases of xiphodynia are reported. Xiphodynia is probably much more common than is generally appreciated and should be included in the differential diagnosis of obscure, unusual, or atypical abdominal or thoracic pain. Once considered, the diagnosis is simple and the treatment dramatically effective in relieving the patient of pain and in obviating the need for a myriad of diagnostic tests and procedures.

Introduction

The xiphoid process is the osseocartilagenous, swordlike protrusion at the end of the sternum that serves as a rigid attachment for various ligaments and tendons of the anterior chest, abdomen and diaphragm. While it is rarely involved pathologically, it may occasionally be the source of a pain syndrome known as xiphodynia. Xiphodynia has been associated with many diverse disorders, including rheumatic, systemic, cardiovascular, gastrointestinal, metabolic, musculoskeletal, and neurologic diseases, but may occur without an apparent underlying cause. The following case reports illustrate the diagnostic difficulty posed by this obscure disorder, the ease of diagnosis when this entity is considered, and the remarkable and gratifying response to appropriate therapy.

Case Reports

Case No. 1

A.D., a 30-year-old stockbroker, developed acute epigastric pain, nausea, vomiting, and diarrhea. The epigastric pain was constant, not influenced by food ingestion, and radiated to the back, shoulders, arms, and chest wall. All symptoms except the epigastric pain abated, and during the following weeks she was treated for peptic ulcer disease, cholelithiasis, myositis, pleurisy, and psychoneurosis. Routine blood tests, urinalysis, erythrocyte sedimentation rate, upper gastrointestinal series, cholecystogram, intravenous pyelogram, barium enema, proctosigmoidoscopy, x-ray films of the entire spine, x-ray film of the chest, and electrocardiogram were normal. Physical examination revealed an exquisitely tender xiphoid process that, when depressed, reproduced the patient's pain in its entirety. She was reassured that xiphodynia is usually a self-limited disease, and her pain gradually subsided in several weeks without therapy.

Case No. 2

C.P. is a 67-year-old female who complained for six months of a constant, agonizing, epigastric and substernal burning pain that radiated to the back, shoulders and neck. It was aggravated by deep breathing, coughing, sitting up, leaning forward and eating. In fact, the pain on eating was so severe that she virtually stopped eating and suffered a 35-pound weight loss. Gastroscopy showed a very mild gastritis, but no significant pain relief was achieved with antacid therapy, including cimetidine. The patient was subsequently admitted to The Mount Sinai Hospital in New York City, where the initial physical examination was said to be unremarkable. An extensive diagnostic evaluation revealed a negative ultrasonogram, an upper gastrointestinal series showing minimal dilatation of the duodenal sweep, a CAT scan suggestive of a pancreatic mass and a pancreatic secretion test revealing a slightly diminished secretory volume. The CBC, platelet count, stool guaiac, ESR, 6- and 12-channel, T-4, cholecystogram, barium enema, electrocardiogram, x-ray film of the chest and a liver-spleen scan were all within normal limits. Because of the unremitting epigastric pain radiating to the back, a 35-pound weight loss, and the results of the upper GI series, CAT scan and pancreatic secretion tests, an exploratory laparotomy was performed for a presumptive diagnosis of pancreatic carcinoma. No pathology was found. Several hours postoperatively, the patient complained of a new type of chest pain, and serial

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From the Department of Medicine, Mount Sinai School of Medicine of The City University of New York, N.Y.

Requests for reprints should be sent to H. J. Sklaroff M.D., 1175 Park Ave., New York, N.Y. 10028.

electrocardiograms, a pyrophosphate scan and serum CPK MB determination established the diagnosis of an acute anteroseptal myocardial infarction. The pain gradually subsided and the patient's subsequent course in the coronary care unit was entirely uncomplicated. However, the original pain was unremitting, the patient occasionally crying out because of its severity. Examination forty-eight hours following the myocardial infarction revealed an exquisitely tender xiphoid process and paraxiphoid region, palpation reproducing in its entirety the patient's pain of the last six months. A diagnosis of xiphodynia was made and ten cc of 2% lidocaine were injected into the affected area in the presence of the patient's husband and son, a nurse and two medical residents. In fifteen minutes the patient was completely relieved of her pain, stating that a miracle had been performed. She was able to sit up, lean forward, cough, breathe deeply and eat a large meal all without pain for the first time in six months. She was discharged from the hospital ten days later, completely free of pain and having gained five pounds.

Case No. 3

P.K. is a 22-year-old white female who complained of a constant anterior chest pain of varying intensity for two months. The pain was aggravated by coughing, deep breathing and leaning forward. Routine diagnostic evaluation, including CBC, urinalysis, electrocardiogram and chext x-ray, was negative. The physical examination revealed tenderness of the xiphoid bone and adjacent areas. 2.5 cc of 1% lidocaine relieved the patient's pain in ten minutes. A subsequent injection of ten cc of 2% lidocaine was given, and the patient has since been pain-free.

Case No. 4

C.Z., a 52-year-old obese woman with extreme anxiety, has had multiple psychosomatic complaints. In June 1978, she complained of several months of anterior chest pain occasionally radiating to the shoulders and back, which was constant, aggravated by change in position, deep breathing and brisk walking, and was most severe in the mornings while travelling by train to her job in New York City's garment center. Physical examination revealed a very tender xiphoid process and paraxiphoid region. Ten cc of 2% lidocaine were injected into the affected area resulting in dramatic relief of her pain which has not recurred.

Case No. 5

C.D., a 67-year-old cook, was a heavy cigarette smoker with a chronic cough. She began to complain of severe chest pain that was constant, bilateral, subcostal, worse with coughing and deep breathing, and especially bad when supine. She had consulted several physicians who performed many diagnostic procedures and prescribed a variety of treatments without success. Physical examination revealed a very tender xiphoid process and paraxiphoid region. Ten cc of 2% lidocaine were injected into the tender areas resulting in prompt relief of the patient's pain. One subsequent injection was necessary, and the patient has since been pain-free.

Case No. 6

A.R., a 53-year-old woman, was referred in 1973 for chest pain that was substernal, induced by effort, slowly relieved with rest, and possibly by nitroglycerine. It also occurred at rest and could last for several hours. During the pain, electrocardiograms revealed definite S-T and T wave changes. The patient had a cholecystectomy in 1952 and removal of wire sutures from the scar in 1973, which relieved her of abdominal pain she had had for twenty years. In 1964, she underwent a total abdominal hysterectomy and salpingo-oophorectomy for a fibroid uterus and heavy vaginal bleeding. In 1974, a stress test revealed no significant electrocardiographic changes, and coronary arteriography and complete cardiac catheterization were normal. During the following three years, the patient continued to complain of severe substernal chest pain lasting many hours and usually associated with S-T and T wave changes. No relief was obtained from propranolol hydrochloride, isosorbide dinitrate, indomethacin, prednisone, or antacids. An infinite number of diagnostic procedures were performed, including abdominal sonography, abdominal CAT scan, intravenous pyelography, intravenous cholangiography, upper gastrointestinal series, esophageal acid infusion test, barium enema, etc., and all were within normal limits. Psychiatric consultation confirmed our impression that the patient had no significant emotional illness. In February 1975, a complete diagnostic evaluation was made at the Mayo Clinic with no explanation of the atypical chest pain forthcoming.

The patient continued to have substernal chest pain requiring the use of narcotics until July 22, 1978. On that day, 15 cc of 2% lidocaine were injected into the lower sternum, xiphoid process and paraxiphoid region, after pressure on those areas seemed to reproduce the patient's pain. She has had two subsequent injections, each affording her dramatic relief, and she has since required no analgesics.

Discussion

Xiphodynia varies in location, quality, severity, duration and radiation, but is usually paraxiphoid, dull, burning or aching, and radiates to the epigastrium, anterior chest, neck, shoulders and/or back. It frequently arises spontaneously or may be produced by trauma or muscle strain. It may be aggravated by bending, lifting, breathing, coughing, sneezing or swallowing, thereby suggesting a host of conditions, especially cardiorespiratory and gastrointestinal diseases. While xiphodynia often occurs in the absence of an associated malady, it has been described in the setting of cardiac disease (angina pectoris, myocardial infarction and pericarditis), gastrointestinal disease (hiatal hernia, esophagitis, esophageal diverticulum, peptic ulcer and cholelithiasis), rheumatic diseases, gout, Paget's disease, pernicious anemia, multiple myeloma, leukemia, hypothyroidism, and disorders of bone, muscle, cartilage and nerve.

A sine qua non of xiphodynia is the reproduction of the patient's pain in its entirety by moderate pressure on the xiphoid bone and its adjacent attachments. Another is the dramatic relief obtained with procaine infiltration into the affected area.

The treatment of xiphodynia includes therapy for the underlying disease, if such exists; reassurance of the patient that the disease usually disappears spontaneously; rarely, surgical removal of the xiphoid bone, should the pain prove intractable; and infiltration of adequate amounts of procaine or a like substance into the xiphoid bone and its surrounding area, this being the simplest and most effective mode of therapy. The mechanism by which procaine produces prolonged and often permanent relief of this pain syndrome is unclear but well documented.

Xiphodynia is probably much more common than is generally appreciated and should be included in the differential diagnosis of obscure, unusual or atypical abdominal or thoracic pain. Once considered, the diagnosis is simple and the treatment dramatically effective in relieving the patient of his pain and in obviating the need for a myriad of diagnostic tests and procedures.

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ST Depression Under Anesthesia in a Patient on Lithium Carbonate

MARGARET G. PRATILA, M.D. AND VASILIOS PRATILAS, M.D.

Abstract

We present a patient, on lithium carbonate, who developed an ST depression, shown on the ECG monitor (and confirmed by ECG tracings) during anesthesia. Possible causes are reviewed. The effects of lithium carbonate on the cardiac cell are discussed and the possible role of droperidol in the production of this ST depression.

Introduction

There have been many reports on the effects of lithium carbonate on the heart. These include conduction blocks, such as sino-atrial (1–3) atrio-ventricular (4) left bundle branch block (LBBB), ventricular irritability (6, 7), myocarditis (6, 8), and flat or inverted T waves (9). Only the patient who developed LBBB was anesthetized at the time of its onset. We report the case of a patient on lithium carbonate who developed S-T segment depression during anesthesia.

Case Report

The patient was a 62-year-old, 73-kg man, who was admitted to the hospital with a history of rectal bleeding and anemia. The diagnosis was carcinoma of the sigmoid colon, confirmed by barium enema. He had a history of manic depressive illness and had been taking lithium carbonate for ten years. He had been stable on a dose of 900 mg twice daily, orally. He had visited his psychiatrist one month previously because of increasing tremor of his hands. At that time many of the signs of Parkinsonism were noted. There was no history of cardiac or pulmonary disease. His diabetes mellitus was controlled with diet. Past surgical history was of a tonsillectomy as a child without problems. Physical examination revealed nothing except for signs of Parkinsonism, unchanged during the month since his visit to his psychiatrist. The blood pressure was 140/80 and the pulse rate was 70 per minute and regular. The chest x-ray and ECG were normal. The hematocrit was 24% and serum electrolytes were sodium, 144 mEq/1; chloride, 110 mEq/1; potassium, 3.9 mEq/1, and lithium 2 mEq/1. The patient was transfused with packed cells, a repeat hematocrit was 33%, and surgical preparation for sigmoid resection was performed.

Pantopon 20 mgm was given one hour prior to induction of anesthesia. Following preoxygenation, 3 mg of d-tubo-curare and 2 ml of Innovar® (droperidol 2.5 mg and fentanyl 0.05 mg/ml) were injected iv. This was followed by sodium thiopental 250 mg and succinylcholine 100 mg iv. Endotracheal intubation with a 9mm ID tube was performed with ease. Anesthesia was maintained with nitrous oxide and oxygen (51:31/minute) and supplemented with intermittent intravenous injections of fentanyl (total dose 0.15 mg), droperidol (total dose 3.75 mg) and d-tubo-curare (total dose 24 mg). Ventilation was mechanically controlled with a tidal volume of 800 ml at a rate of 14 breaths/min. The ECG showed a regular sinus rhythm with complexes unchanged since presurgery.

One and one half hours after the induction of anesthesia, (surgical time, 1 hour 15 minutes) and 20 minutes following the last dose of droperidol and fentanyl, an increasing ST depression was noted on ECG (Fig. 1). There was no change in heart rate, rhythm or blood pressure. Arterial blood gases measured at this time were pO_2 105 mm Hg, pCO_2 38 mm Hg pH 7.41 HbO_2 98%. The ST depression persisted for 35 minutes and then gradually returned to baseline over the next 10–15 minutes. Surgery was completed after another 30 minutes. Atropine 1.2 mg iv was used for reversal and the patient was extubated.

In the recovery room the patient remained stable, with no alteration in pulse rate, in blood pressure, or in the ECG reading. Postoperatively, serial ECGs were normal and serum enzymes were within normal limits. Exercise test showed no ischemia.

From the Departments of Anesthesiology, Beth Israel Medical Center and Mount Sinai School of Medicine, of The City University of New York.

Requests for reprints should be sent to M. Pratila, M.D., 150 East 69th Street, New York, New York 10021.

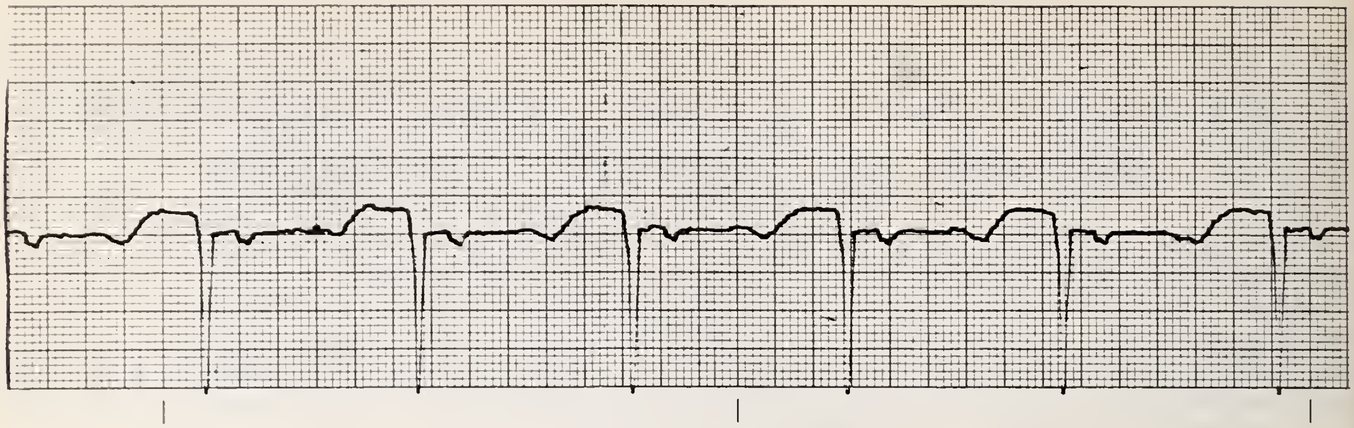

FIG. 1. ECG showing 4mm ST depression.

Discussion

The ST segment of the ECG occurs during systole when all regions of the ventricle are in a depolarized state. Normally, the potential of the ECG is the same as that during the TP interval and reflects the absence of potential differences within the ventricle. During the TP interval, however, the ventricles are fully repolarized. The long duration of the ST segment reflects the normally prolonged plateau (phase 2) of the cardiac action potential. A shift in the ST segment (the TP interval is assumed by convention to represent zero potential) may represent the abnormal presence of a region of nonexcited tissue in the ventricles during systole or the abnormal persistence of depolarization in a portion of the ventricles during diastole (10).

Carmeliet has shown, during intracellular microelectrode and ion movement studies in calf Purkinje fibers and cat ventricular myocardium exposed to lithium, that there is a decrease in the rate of diastolic depolarization, probably caused by an increased membrane permeability to potassium. Lithium appears to affect the cardiac conducting system by incomplete substitution for other cations. As in other cells, lithium and sodium readily enter the cardiac cell but lithium is not effectively removed (11). Lithium replaces some intracellular potassium which then diffuses into the surrounding medium (12). There is a delayed decrease in the mean resting potential as a result of a fall in intracellular potassium and a late decrease in amplitude and duration of the action potential. This is caused by a falling (more positive) membrane potential and an increasing rate of repolarization–both caused by pronounced intracellular potassium depletion in conjunction with an increased rate of potassium efflux.

Lithium may also interfere with the actions of hormones such as the catecholamines that affect excitability. Animal studies have shown that lithium alters myocardial carbohydrate utilization before the appearance of conduction abnormalities, and partially inhibits the pressor effects of norepinephrine. Lithium may produce these effects by interfering with catecholamine stimulation of adenyl cyclase to produce cAMP (13).

Horgan et al (14) found that lithium increased the myocardial contractility in intact dogs, and they advanced the hypothesis that accumulating lithium intracellularly could cause an increase in the concentration of free calcium, which in turn could be responsible for this effect. This is supported by the work of Nielson-Kudsk and Kirstein Pedson (15). They believe it is possible that lithium, by lowering the resting membrane potential and by an early prolongation of the duration of the plateau (phase 2) of the action potential, may cause an increase of cellular influx of calcium during this phase. Others (16, 17) have also stated that this increased rate of intracellular liberation of calcium ions from mitochondria, from the sarcoplasmic reticulum, and possibly from internal membraneous binding sites seems to be a possible mechanism of action of lithium. A possible weak inhibitory action on the sodium-potassium pump related to the cell membrane could be an additional factor causing intracellular calcium liberation (15).

We can assume the ECG changes we describe to be the result of an influx of lithium into the cells causing a fall in the resting potential with a delay in repolarization and resultant ST depression. Asymmetry of conduction can be detected in any bundle of normal cardiac fibers. It is not surprising that any agency that depresses excitability, such as a high potassium ion concentration outside the cell and an increased calcium ion concentration inside the cell, will exaggerate these preexisting asymmetries (18).

Hauswirth (19) has shown in isolated sheep Purkinje fibers that droperidol increases the effective refractory period and decreases the speed of phase 0 depolarization. This has been supported by the work of Kern et al (20) who reported that droperidol prolongs the functional refractory period by inhibiting the sodium carrying system. It is possible that the ST depression occurred in our patient because of potentiation of the action of lithium by the addition of droperidol.

Another interesting facet of the ST depression is in its differential diagnosis, particularly from myocardial ischemia. Since the ST depression cleared quickly, and there were no changes in blood pressure or pulse rate, the benign postoperative course makes this diagnosis unlikely in retrospect, but a valid concern during the operative period.

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A Framework for Participation: The Contribution of a Medical School to Local Health Planning*

SAMUEL J. BOSCH, M.D., ELLEN FISCHER, B.A., AND KURT W. DEUSCHLE, M.D.

Medical schools have always exerted an influence on the organization and delivery of health care through the physicians they train and the hospitals they use. Cecil Sheps, in 1977, noted that the 117 medical schools in the U.S. are affiliated with more than 400 teaching hospitals that together account for 25% of the acute care beds in the nation (1). Under these circumstances, medical schools cannot but have a significant impact on the current and future organization of the health care system.

The age-old debate within the medical community—whether influence should continue to be exercised indirectly or should also be expressed directly, with medical schools acting as agents of change–seems to be resolving itself in favor of the latter, at least for the time being, as witnessed by the university-based neighborhood health center movement of the 1960s and university involvement in the HMO movement of the 1970s. With the advent of the National Health Planning and Resources Development Act of 1974, the de facto role of medical schools has become de jure as well. Stipulating that health professional schools in an area be represented on the HSA Board, PL 93-641 has assured the direct input of medical schools into local health planning.

Participation in change on the part of a medical school is not always self-initiated, however. In this era of consumerism, community groups–consumers, providers and local agencies such as the HSAs–are reaching out with increasing frequency for the technical assistance a medical school can offer, particularly in relation to program planning and evaluation. Logically enough, the community's initial contact with the resources of the medical school and medical center is often through a department of community medicine. Experience has shown that a medical school or department that accepts the responsibility to work with the community on its initiative, particularly in urban areas, can expect to receive more requests than it can possibly handle. To be successful, a medical school (and especially an individual department acting as liaison for the medical school) attempting to contribute to planned change in an urban setting must be firmly rooted and must have a strong enough sense of itself to establish its priorities and stick with them. Failing this, the complexity of urban health issues and the variety of ways in which the community may request intervention in them may be so overwhelming as to swamp the best of intentions and leave a school or its liaison department floundering.

Over the past ten years, Mount Sinai School of Medicine has had ample opportunity to test this conviction. Experience in working toward change in the East Harlem health care network indicates that to contribute meaningfully a school must be able to identify and pursue the most appropriate opportunities among those available to it so as to avoid overextending its resources. In turn, at least three elements are essential in handling this process successfully: 1) a well-defined institutional goal, 2) a carefully conceived and articulated set of working rules to guide the school's efforts and to provide a framework for its planning and development activities, and 3) a well-developed sense of patience. The overall goal, of course, provides a context within which to determine the appropriateness of taking part in any proposed endeavor, while the working rule serves as a quick standard against which to evaluate and assign priorities to relevant programs and projects. Patience and the recognition that in a democratic and pluralistic society real change occurs slowly, diminish the tendencies toward frustration and disillusionment confronting any group anxious to affect the way health care is organized and delivered in the U.S.

The Department of Community Medicine at Mount Sinai has adopted this approach to local health planning,

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From the Department of Community Medicine, Mount Sinai School of Medicine, of The City University of New York, New York N. Y.

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and its decade of experience may prove instructive for other institutions considering participation in this arena.

The Framework at Mount Sinai

Since its creation in 1968, Mount Sinai School of Medicine, primarily through its Deparment of Community Medicine, has worked with the surrounding community, East Harlem, to improve the organization and delivery of health care in the area (2). East Harlem is a predominantly low-income, medically underserved community located in the northeastern corner of Manhattan. Of its approximately 150,000 residents, some 45% are of Hispanic origin, 35% are Black, and 17% are whites of direct European ancestry.

From the outset, the founders of the medical school made the identification and solution of community health problems a clear institutional goal (3, 4). Recognizing that this social commitment would be meaningless unless it could be translanted into a critical mass of full-time community health scientists working alongside the school's basic scientists and clinical scientists, a generously endowed Department of Community Medicine was established that provides an essential resource for medical education, service and research.

One of the department's principal mandates is to serve as a bridge between the resources of the medical center and those of East Harlem. Engaging in joint problem-solving efforts with the community, the department has further refined the institutional goal by adopting a set of six working rules to guide its involvement in community health planning and development activities:

1) To participate with a variety of community groups (consumers and providers) in improving health care services in the area without assuming direct responsibility for the administration and/or actual provision of health care services. This is without a doubt the central, overriding tenet of the department's community health practice.
2) To promote the coordination and integration of health care services, that is to say, the regionalization of delivery programs, taking into consideration the pluralistic nature of our society.
3) To foster population-based planning, concentrating on adapting the existing health care system to the needs of defined groups within the population, and avoiding the tendency to work entirely within the existing institutional framework.
4) To encourage the delivery of health care through organized group practice health teams encompassing not only a variety of medical specialists, but other health professionals and paraprofessionals.
5) To promote the financing of health care by prepayment and capitation.
6) To encourage provider groups to assume full responsibility for maintaining the health of well defined population groups.

The health care delivery network in East Harlem, as in any other medically underserved area, is fragmented, duplicative, uncoordinated and inefficient. At any one time the number of serious health problems and organizational issues demanding immediate attention is overwhelming. Each of the community-based groups that has approached the department requesting technical assistance in addressing one or more of these interrelated issues has its own set of priorities and long-term goals, and most would gladly see all the technical resources of the department deployed for the attainment of their goals. In such a situation, a department that did not have a clear notion of what it was trying to accomplish could easily find itself being pulled in several directions at once.

By using the previously described guidelines to categorize and prioritize requests for technical assistance in program planning, development and evaluation, the Mount Sinai Department of Community Medicine has been able to resist the pressures to immerse itself in the legitimate but diverse concerns and enthusiasms of various groups in the community, and to be thus seriously sidetracked from the pursuit of its own overall goal. Having programmatic criteria for responding to particular community requests has allowed it to contribute to the development of an orientation toward regionalization among both consumer and provider groups in the area, and to encourage the community's sense of its capacity to identify and meet its own needs. The department's contribution has been made through a series of projects, each influencing the availability, accessibility and/or quality of care in the area, and each furthering in some way the community's movement toward a more rational organization of care. A few of these programs will be summarized here to exemplify the ways in which the Department has interpreted and applied its six working rules.

In response to a request from the East Harlem Council for Human Services (EHCHS), a Puerto Rican community organization, the department participated in considering alternative approaches to the provision of comprehensive health care in East Harlem. As an outgrowth of these discussions the EHCHS decided to establish and operate a neighborhood health center. Departmental staff worked with the EHCHS to develop and implement all phases of the Center's program, which was designed in such a way that, in the future, the Center could be converted into the core group of a health maintenance organization (HMO).

The Center now offers comprehensive primary care and related support services to a registered population, primarily from East Harlem. It is linked to the Hospital for Joint Diseases for secondary back-up, while The Mount Sinai Hospital provides specialty and subspecialty ambulatory and inpatient care for Center registrants. The facility is located in the Taino Towers, a low-income residential and human-services complex, where it is able to serve a population of 40,000. The EHCHS continues to subcontract with the department for technical assistance in the ongoing evaluation of the Center's activities, in data analysis, and in program planning efforts.

Given its long-standing partnership with the staff of the EHCHS Neighborhood Health Center, the department is in a position to encourage their assumption of responsibilty for maintaining the health of a defined population group. As the Center moves to arrange for financing by capitation, which it is ready to do in principle, its potential for achieving this will be greatly enhanced.

At the request of the Hospital for Joint Diseases (HJD), a voluntary hospital in the northern part of East Harlem, the department is collaborating in the redefinition of the Hospital's role in the changing community health care delivery network. Staff members are working with HJD staff to reexamine the institution's goals and objectives as it moves through the various stage of its conversion from a primarily orthopedic institution to a community hospital with close formal ties to other provider institutions in East Harlem and Central Harlem. In addition, staff from the department have lent their technical expertise to the development of a hospital-based group practice to replace HJD's existing ambulatory care services. Participation in these efforts affords an opportunity to strengthen the relationship between the Hospital for Joint Diseases and the EHCHS Neighborhood Health Center, as well as to improve the overall availability and accessibility of high quality care in East Harlem.

Over the past five years the Department has responded to a series of requests from community groups to participate in efforts to improve health care for school-aged children in the area. An interdisciplinary team from Community Medicine, together with representatives of the local schools, the NYC Board of Education, and local officers of the Department of Health and the Department of Social Services, explored alternate means of exploiting the full potential of existing resources for prevention, diagnosis and treatment of the health problems of this population group. The results of the deliberations and initial experiences of this interagency group are reflected in the prepaid health care plan developed by them, a model designed to assure access to health care services for school-aged children and their families in East Harlem, or any other inner-city area (5).

The proposed plan, inspired by the marketing-through-employment approach of the Kaiser-Permanente system, considers the inner-city school an organizational structure analogous to the workplace and calls for enrollment to be offered to families through the schools, with the cooperation of the school administration. Reimbursement to providers is on a capitation basis. An interinstitutional effort is now under way to implement the model and, in particular, to test the proposed administrative structure responsible for 1) financing health care, 2) monitoring the organization and quality of services, and 3) establishing and maintaining effective linkages between funding agencies, local agencies responsible for school health, local providers of care and East Harlem consumers. The model is designed to become an independent, community-governed and community-run, regional program.

Because Mount Sinai School of Medicine serves as the operational base for the Department of Community Medicine and is financially and administratively independent of The Mount Sinai Hospital, we have been able to respond to requests for technical assistance from the Hospital itself, which we consider another provider group within the East Harlem community. Thus, for example, when the Hospital recognized a need to reorganize certain aspects of the ambulatory care services, a team of organizational sociologists from the department was assigned to work with hospital staff in addressing these problems. This team is now involved on an ongoing basis in concurrent evaluation activities within the institution.

Although the department is the mandated liaison between the medical school and its surrounding community, as federal emphasis on epidemiologic approaches, community issues, and regionalization has increased, other departments have encountered a growing impetus to expand their efforts beyond the confines of the hospital-medical school complex. In many instances the department has been called upon to participate in these expanded programs because of its capacity to facilitate the development of an effective working relationship with community groups and the technical expertise it can lend in community-based program planning. The willingness of other departments to organize cooperative efforts reflects a recognition of the distinct contributions the clinical and community science faculties have to make to the improvement of health care services. This appreciation has emerged over time as the outcome of ongoing dialogue, participation in common educational efforts and working together on an equal basis on medical school and hospital committees, and has resulted in a variety of joint programs between the Department of Community Medicine and the departments of medicine, pediatrics, obstetrics, surgery, psychiatry and dentistry focusing on issues in health care delivery as well as categorical problem areas such as early detection of impairments and disease.

An outstanding example of such efforts is the recently funded Pediatric Pulmonary Center at Mount Sinai. The Department of Pediatrics drew upon the Department of Community Medicine as well as other departments in the medical center in conceptualizing a program to coordinate existing clinical, educational and research activities to provide the best possible regionalized care for infants and children susceptible to or suffering from chronic pulmonary disease, and to foster educational and research activities to assure the continued provision of optimal care in the future. As this program is implemented, Community Medicine staff members will be integrally involved in each of the three primary program components: service, training, and research. They will participate in the training of current providers, future providers (both medical students and residents), and consumers of care; they will offer opportunities for field studies in occupational pulmonary disease under the aegis of the Department's Environmental Sciences Laboratory; and they will be responsible for concurrent evaluation of the Center's activities, for the development of linkages with those institutions that may serve as referral sources for the Center, and for handling community outreach activities.

Although the goals of the projects that have been described are as diverse as the groups which sponsor them, there are common threads that unite them. The unifying theme is provided by the department's guidelines; the decision to participate in each project was based on a recognition of a common foundation: a shared belief in the need for regionalized care, community participation, population-based planning, group practice health teams, prepaid capitation and/or the assumption of responsibility for the maintenance of good health.

This set of guidelines is, of course, used not only as a framework for accepting and assigning priorities to requests from the community, but for ruling out participation in certain types of projects and programs as well. There are primarily two kinds of activities in which the department declines participation: out-of-area efforts and those that are inappropriate in terms of its stated goals. When, for example, the Universidad Javeriana in Bogota, Colombia, requested help in assessing the feasibility of a prepaid group practice health plan the department accepted only a very limited consultorial role while at the same time helping to bring the university people together with local groups that had expertise in health planning. Similarly, when groups from East Harlem are interested in the direct provision of services beyond the scope of the department (such as education around specific health problems), care is taken to clarify why there can be no involvement, and to put them in touch with a group or agency, inside or outside the medical school-hospital complex, able to respond to their requests.

Conclusions

The question now facing medical schools and the individual departments within them is not whether they should attempt to influence the changing course of health care delivery in the U.S. or not. By virtue of their most common activities, medical schools are inevitably caught up in the reshaping of the health care system. The issue that remains, particularly for those institutions committed to working with community groups, is how they can assure that their influence is felt as a contribution to planned change. The Mount Sinai experience illustrates one apparent solution to this dilemma.

That it is necessary to carefully define goals and objectives in order to operate effectively in this arena may seem obvious. However, at the risk of belaboring the point, if an institution is to withstand the pressures of conflicting priorities and focus its activities to pursue simultaneously its own vision, it is essential that departmental aims be explicitly and consciously articulated. An unspoken but presumed agreement by departments and/or staff members on priorities and goals is not sufficient to provide the type of framework discussed. Rather, it is felt that the explicit formulation of working rules is a crucial (albeit not wholly sufficient) factor in developing a long-term capacity to contribute meaningfully to planned change in the health care system.

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Recurrent Diverticulitis After Conservative Surgery

ELLIOT MAYEFSKY, M.D., ARTHUR SICULAR, M.D., F.A.C.S., and W. JOHN B. HODGSON, M.S., F.R.C.S.*

Abstract

Symptomatic recurrent diverticulitis is increasingly appearing during the fourth and fifth decades. To deal with symptomatic younger patients, newer surgical approaches have been proposed in recent years. In 1964, Reilly introduced the concept of longitudinal sigmoidomyotomy in the surgical management of diverticular disease. Procedural complications were frequent with this either intraoperatively or postoperatively. As an alternative to the Reilly myotomy, the transverse taeniamyotomy was presented by Hodgson in 1973. Two recent reports present early success with this procedure in selected patients. This report presents two cases in which diverticulitis recurred after transverse taeniamyotomy. One patient required reoperation for a recurrent inflammatory mass which was proximal to the site of his previous taeniamyotomy. The second patient has had two subsequent episodes of diverticulitis but the sites of these recurrent attacks are not known. Since the recurrent inflammation occurred, proximal to the myotomized area in the reoperated case, this would suggest that as a method of preventing continuation of symptoms from diverticular disease, transverse taeniamyotomy could only be expected to succeed when done from rectosigmoid well up the descending colon to encompass all areas of contraction and hypertrophy.

Introduction

Symptomatic recurrent diverticulitis is increasingly seen during the fourth and fifth decades. Its significant morbidity often requires hospitalization for management. Surgery has traditionally been reserved for complications such as fistula formation and extramural abscess. To deal with symptomatic younger patients newer surgical approaches to the problem have been proposed in recent years.

In 1964, Reilly introduced the concept of longitudinal sigmoidomyotomy in the surgical management of diverticular disease. Based on the idea that spasm of the sigmoid smooth muscle is fundamental to the development of diverticulitis, surgery involved cutting the circular muscle of the sigmoid along an antimesenteric taenia. It was believed that this would reduce the vigor of smooth muscle contractions and lessen spasm and intralumenal pressure.

To be effective, the myotomy had to reach the submucosal layer of the bowel cutting all circular fibers. Procedural complications including hemmorrhage from submucosal blood vessels, and perforation of the bowel were frequent either intraoperatively or postoperatively. It was therefore recommended that a protective cecostomy be performed with myotomy while healing took place (1).

As an alternative to the Reilly myotomy, the transverse taeniamyotomy was presented by Hodgson in 1973 (2). In this procedure, the two antimesenteric taenia of the sigmoid are cut at two centimeter intervals beginning at the rectosigmoid junction, where the taenia are fused, and are continued across the diseased segment to normal bowel. By cutting the taenia in this way, it is felt that the bowel will lengthen and the necks of the diverticula will widen permitting them to decompress into the bowel. In addition, the effectiveness of the circular muscle contractions will be lessened since the taenia will no longer serve as guys for circular muscle contraction. Thus the degree of sigmoid spasm will be reduced, intrasigmoid pressures will be less, diverticula will decompress, and the setting for diverticulitis will diminish.

Based on the above hypothesis, transverse taeniamyotomy has been used in selected cases as one surgical alternative in the treatment of painful diverticular disease unresponsive to medical management. Two recent reports present early success with this procedure. Pescatori and Castiglioni reported improvement in twelve patients with sigmoid diverticular disease (3). Their indications for transverse taeniamyotomy included severe pain and constipation, absence of any inflammation or perforation, the presence of sigmoid shortening with thickened muscle and high intralumenal pressures, and

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From the Departments of Surgery, The Mount Sinai Hospital and the * Bronx Veterans Administration Hospital New York, N.Y.

Reprint requests should be sent to Dr. E. Mayefsky, Box 586, The Mount Sinai Hospital, New York, NY 10029.

failure of medical treatment. Another report by Hodgson et al presented success in four patients with localized diverticulitis (4). They showed that transverse taeniamyotomy could successfully be used in selected cases with acute inflammation.

This report presents two cases, from The Mount Sinai Medical Center and the Bronx Veterans Administration Medical Center in New York City, in which diverticulitis recurred after taeniamyotomy.

Case 1

The patient was a 34-year-old Latin male whose abdominal symptoms dated back to 1970 when he had epigastric pain and rectal bleeding. A sigmoidoscopy to 15 cm as well as a barium enema were normal. He was again seen in June 1976 with a two-day history of right lower quadrant abdominal pain that worsened by movement and constipation. An examination revealed a fever and marked right lower quadrant tenderness. There was a leukocytosis with a left shift. The patient was taken to the operating room with a preoperative diagnosis of acute appendicitis. At laparotomy the sigmoid colon was found to lie in the right iliac fossa and was acutely inflamed. There were 150 cc of seropurulent material in the peritoneal cavity. The appendix was normal. The right lower quadrant was drained and a loop transverse colostomy made. Recovery was uneventful and two weeks later a barium enema was performed that showed marked diverticular disease of the entire sigmoid. After referral, the patient was taken to the operating room where sigmoid diverticulitis superimposed on diverticular disease was seen. A transverse taeniamyotomy and a limited sigmoid resection was performed. Postoperative recovery was again uneventful and the transverse colostomy was closed seven weeks later. On follow up after discharge the patient complained of occasional left lower quadrant pains. A barium enema performed one year later showed residual diverticula in the remaining sigmoid. In July 1978, the patient was admitted with a twenty-four hour history of severe left lower quadrant abdominal pain and constipation. On examination, the patient was febrile and had marked left lower quadrant tenderness. The white blood cell count was 15,300. The patient was placed on intravenous fluids and his pain and leukocytosis subsided, but a left lower quadrant fullness could now be felt. A barium enema showed sigmoid diverticula with minimal spasm. The patient was taken to the operating room where recurrent diverticulitis with an inflammatory mass was seen 7 cm proximal to the previous anastomosis. The mass was also proximal to the previous perianastomotic taeniamyotomy. A left hemicolectomy was performed and included the previous anastomosis. Postoperative recovery was smooth and the patient was discharged. He has subsequently remained asymptomatic.

Case 2

H.J. was a 46-year-old obese woman whose first attack of diverticulitis occurred in 1966. She was treated at that time with intravenous antibiotics with improvement. Left lower quadrant pain recurred in 1976 and again the diagnosis of diverticulitis was made and she was successfully treated with intravenous antibiotics. Four months later the patient underwent an elective cholecystectomy for symptomatic cholelithiasis. At laparotomy, sigmoid diverticulitis with multiple pericolonic adhesions was found. These adhesions were lysed and a transverse taeniamyotomy was performed. In May 1978, two years after the taeniamyotomy, the patient experienced her third episode of acute diverticulitis with left lower quadrant abdominal pain, fever, and leukocytosis. She was managed with an oral antibiotic on an outpatient basis and improved. In June 1979, the patient was admitted to The Mount Sinai Hospital with severe left sided abdominal pain, fever, and shaking chills. On examination she was found to have a left lower quadrant fullness and left upper quadrant tenderness. She had a leukocytosis with a left shift. An obstructive series showed no free air and a generalized ileus pattern. The diagnosis of recurrent acute diverticulitis was made and the patient was placed on intravenous antibiotics with resolution of her symptoms. An ultrasonogram showed no intraabdominal abscess and an intravenous pyelogram was normal. No barium enema was performed. The patient was discharged on an oral antibiotic and a low residue diet. She has continued to have occasional left lower quadrant abdominal pains but has not required repeat hospitalization.

Discussion

Diverticular disease of the sigmoid has been studied in vivo and in vitro. Arfwidsson and Lehmann studied surgical specimens of sigmoid colons removed for diverticular disease and found that there is a true hypertrophy of the circular and longitudinal smooth muscle (5). To study the sigmoid in vivo, open-ended polyethylene tubes have been inserted into the rectum and intracolonic pressure activity measured. Attisha and Smith found that the basal pressure wave and motor activity in the sigmoid in diverticular disease was no different from that in controls (6). In response to physiologic (gastrocolic reflex after a meal) and pharmacologic (Prostigmine) stimulation, however, the diseased sigmoid showed an exaggerated increase in pressure wave and motor activity. After a longitudinal myotomy, there was a significant reduction in the amplitude of the recorded pressure waves. Unfortunately the longitudinal myotomy is difficult to perform without significant morbidity and mortality. The pathophysiologic approach may help the difficult problem of diverticulitis, however, and represent a step forward.

There are two distinct categories of diverticular disorder. Commonly found asymptomatic diverticula, as in diverticulosis, do not concern us. However, in the second category of symptomatic disease it is possible that the formation of sigmoid diverticula results from the combination of muscular thickening and increased motor activity. The thickened taenia and circular muscles causes shortening of the colon and the mucosa is thrown into multiple folds producing small compartments, or cisternae, which partially obstruct the sigmoid lumen. Within these compartments, increased muscle activity is able to generate high intralumenal pressures that are said to cause herniation of the mucosa along the perforating blood vessels. Thus the diverticula are pulsion diverticula that may occur as a secondary response to the muscular thickening and increased motor activity seen in diverticular disease. When the neck of the diverticulum becomes blocked by a fecalith inflammation, an abscess develops and the clinical picture of acute diverticulitis ensues.

The transverse taeniamyotomy was proposed as a way to reverse some of these pathophysiologic changes. Upon cutting the two antimesenteric taenia at regular intervals along the diseased sigmoid the colon lengthens and dilates (4). As the colon lengthens the necks of the diverticula should open allowing them to drain into the bowel lumen. Once cut, the taenia no longer function as effective guys supporting the contraction of the circular muscle coat and so the extremely high intracolonic pressures normally seen in diverticulitis should no longer be generated. This is supported by data presented by Johnson working with the New Zealand White Rabbit (7). He found that after taeniamyotomy there was a marked reduction in the motility index (sum of products of strength and duration of each contraction in standard time). This reduction was most pronounced with increased strength of colonic stimulation. Pescatori and Castiglioni found a similar reduction in patients after transverse taeniamyotomy (3). The changes produced by taeniamyotomy should be lasting since upon healing the cut ends are joined by scar tissue which maintains the lengthening. It is in this setting that the transverse taeniamyotomy has been introduced as one surgical approach in the management of symptomatic diverticular disease.

This report presents two cases in which symptoms recurred following transverse taeniamyotomy. One patient (H.A.) required reoperation and a left hemicolectomy for a recurrent inflammatory mass. This mass was proximal to the site of his previous surgery, however. The other patient (H.J.) experienced two subsequent episodes of diverticulitis requiring antibiotic therapy. The sites of these recurrent attacks of diverticulitis are not known.

In the surgical treatment of diverticulitis, the main body of opinion supports resection of the sigmoid colon. Because of the well known incidence of recurrent disease, particularly in young people after resection, one school of thought advocates extensive resection in diverticulitis from rectum well up the descending colon (8). Naturally the operation becomes more difficult following this approach. On the other hand, the conservative approach, using the transverse taeniamyotomy with, or without, resection apparently reduces morbidity but has not prevented recurrent diverticulitis. Since this recurrent inflammation occurred proximal to the myotomized area in the reoperated case presented here, this would suggest that the taeniamyotomy was not done over a sufficiently long distance of bowel. As a method of preventing continuation of symptoms from diverticular disease, transverse taeniamyotomy could only be expected to succeed when done from rectosigmoid well up into the descending colon to encompass all areas of contraction and hypertrophy.

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The Left Renal Vein

RAJACHANDRAN SRINIVASAN, M.D.

Abstract

In 120 dissected human cadavers, major left renal vein anomalies were found in only 11.6% of the bodies. The most common anomalies were the circumaortic venous ring and retroaortic left renal vein. These anomalies were invariably associated with multiple renal arteries either unilaterally or bilaterally. The clinical and developmental significance of these anomalies is discussed.

Introduction

Precise knowledge of the congenital anomalies of the left renal vein is essential for the proper performance of preoperative procedures such as Venacavogram, renal and adrenal venography. Moreover, since the left kidney is often used for transplants, the surgeon should be aware of the normal anatomy with emphasis on the congenital variations of the venous drainage from the left kidney. Though congenital anomalies of the left renal vein have been reported by many authors (1–4), the purpose of this study is to elucidate some of the common anomalies of the left renal vein on an embryologic anatomical basis in view of the clinical importance of such anomalies.

Materials and Methods

One hundred and twenty cadavers were dissected. In each cadaver, the total arterial blood supply and venous drainage of both the right and left kidneys was demonstrated by dissection. Four measurements were made: 1) the distance (A) between the termination of the left renal vein in the inferior vena cava (IVC) and the termination of the left suprarenal vein in the left renal vein; 2) the distance (B) between the termination of the left renal vein and the termination of the left gonadal vein in the left renal vein; 3) the angle (a) between the left renal vein and the termination of the left suprarenal vein in the left renal vein; and 4) the angle (b) between the left renal vein and the left gonadal vein.

Development of the Left Renal Vein

The development of the left renal vein is asociated with the development of the inferior vena cava. Three pairs of longitudinal veins, the posterior cardinals, subcardinals and the supracardinals drain the dorsal body wall (Fig. 1). Anastomosis between these veins, together with atrophy of certain segments of these anastomotic channels, results in the subsequent development of the inferior vena cava and the left renal vein.

The Posterior Cardinal Veins

These veins are observed as early as the 12–13 somite stage of the developing embryo. The posterior cardinals (PC) lie dorsolateral to the developing mesonephros and extend from the duct of cuvier to the caudal part of the embryo (Fig. 1). A ventral anastomosis forms between the bilaterally situated PC veins anterior to the developing caudal artery. At a later stage, the posterior cardinals are joined on each side by the subcardinals and the supracardinals successively. That portion of the right PC vein between the right supracardinal and the common cardinal veins ultimately transforms into the terminal part of the vena azygos in the human. Eventually, the two posterior cardinals disappear by about the seventh week of the embryonic life.

The Subcardinal Veins

The subcardinal system of veins develops bilaterally slightly later than the posterior cardinals along the medial border of the urogenital fold (Fig. 2). The subcardinals (Sub C) drain into the already developed posterior cardinals, both caudally and cephalically, and eventually replace the posterior cardinals as the effective venous drainage. Anastomotic channels then develop between the right and left subcardinals to form the intersubcardinal anastomosis by about the 11 mm stage of developing embryo. This anastomosis conveys blood from the left side to the developing renal and prerenal segment of the inferior vena cava. The right subcardinal cephalic to the intersubcardinal anastomosis joins with the hepato-

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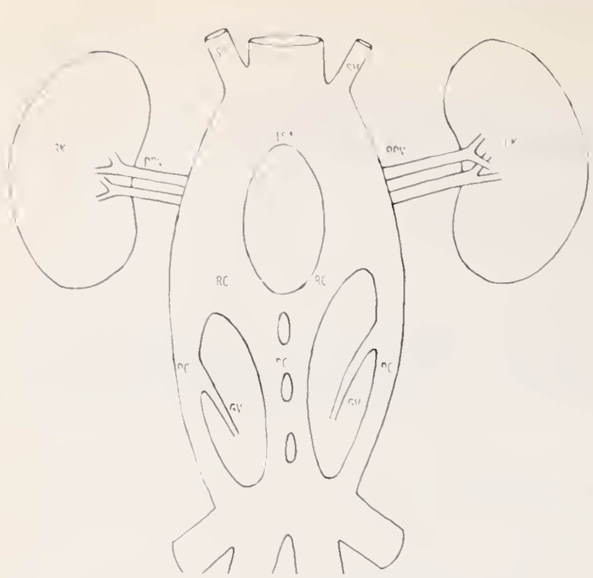
From the Department of Anatomy, Mount Sinai School of Medicine of The City University of New York, New York, N.Y. 10029, U.S.A.

Requests for reprints should be sent to Dr. R. Srinivasan, Department of Anatomy, Mount Sinai School of Medicine, 100th Street and Fifth Avenue New York, N.Y. 10029.



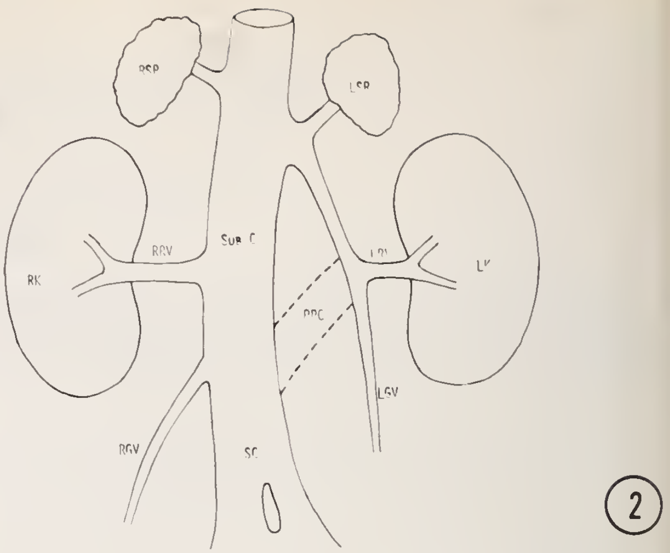


FIG. 1. Development of the renal collar (RC).
FIG. 2. Development of the normal left renal vein (LRV) and atrophy of the dorsal limb of the renal collar (PRC).
* (Fig. 1 and 2 are modified and adapted from Huntington and Mclure 1920, Anatomical Record).

cardiac channel to form the hepatic segment of the inferior vena cava. Eventually, the subcardinal veins contribute to the formation of the inferior vena cava, adrenal veins and the gonadal veins and the intersubcardinal anastomosis forms the major part of the left renal vein.

The Supracardinal Veins

The supracardinal veins (SC) appear bilaterally in the dorsal body wall lateral to the dorsal aorta and the subcardinals (Figs. 1, 2). The supracardinals anastomose with the posterior cardinals and the subcardinals bilaterally. The suprasubcardinal anastomosis on the right side, together with a portion of the right supracardinal vein, forms the post renal portion of the inferior vena cava. The corresponding segment of the left supracardinal vein normally atrophies.

Renal Collar

The renal collar (PRC) that surrounds the aorta is prominent by the 20 mm–22 mm stage of the developing embryo (Fig. 2). It is formed ventrally by the intersubcardinal anastomosis, dorsally by the intersupracardinal anastomosis, and laterally by the supracardinal and subcardinal anastomosis. The developing kidneys each have a primitive dorsal and ventral renal veins draining into the lateral portions of the renal collar. At a later stage the left lateral part of the renal collar atrophies; whereas, the right portion persists as the renal portion of the inferior vena cava. The retroaortic part of the collar together with the left dorsal primitive renal vein disappears.

In conclusion, the left renal vein is developed by the contributions from the primitive ventral renal vein, intersubcardinal anastomosis that receives the suprarenal and gonadal veins; and the left lateral portion of the renal collar.

Results

In 106 out of 120 cadavers, the left renal vein exhibited little variation. The vein was preaortic in position and received the terminations of the left suprarenal vein and the left gonadal vein. The distance (A) between the points of termination of the left renal vein in the left renal vein and the termination of the left renal vein in the inferior vena cava was about 3.12 ± 0.6 cms and the range was between 1.9 and 4.5 cms (Fig. 3). The average distance (B) between the termination of the left gonadal vein in the left renal vein and the termination of the left renal vein was 4.1 ± 0.83 cms with a range between 3 cms and 6.5 cms (Fig. 3). The angle of termination of the left suprarenal vein into the left renal vein was on the average about 115° with a range between 90° to 140°. The angle (b) of termination of the left gonadal vein was about 122° with a range between 90° and 160°.

Out of the remaining 14 cadavers, ten exhibited a complete circum aortic venous ring, three cadavers had retroaortic left renal veins and one cadaver had had a double inferior vena cava.

Anatomical Description of the Anomalies

Circumaortic Venous Ring

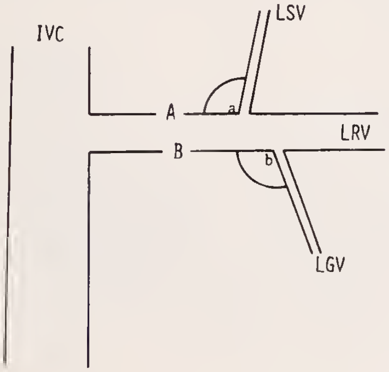
Figure 4 depicts the dorsal limb (PRC) of the Circumaortic Venous (CAV) ring formed by a slender vein descending obliquely from the left renal distal to the left gonadal vein, dorsal to the abdominal aorta at the level of the disc between the second and third lumbar vertebrae and terminating in the IVC about 2.5 cms below the termination of the left renal vein. The ventral limb (LGV) of the CAV ring received the left suprarenal vein. Five renal arteries were present on the right side, each having an independent origin from the abdominal aorta. The right renal vein (RRV) was normal.

In Figure 5, the dorsal limb (PRC) of the CAV ring is formed by an oblique vein arising from a tributary of the renal vein and terminating in the IVC about 5.5 cms below the termination of the ventral limb. This vein passed dorsal to the abdominal aorta at the level of the lower border of the third lumbar vertebra. The lower renal artery on the left side ascended to the hilum of the left kidney at an angle of 135° from the abdominal aorta. The upper artery was normal in position. The two right renal arteries (RRA) passed dorsal to ther inferior vena cava.

In Figure 6, the dorsal limb (PRC) of the CAV ring crossed behind the abdominal aorta at the level of the upper border of the third lumbar vertebra and terminated in the IVC about three cms below the termination of the ventral limb. The left gonadal vein drained into the dorsal limb. There were two independent renal arteries (LRA) on the left side.

Figure 7 shows the dorsal limb (PRC) of the CAV ring is formed by an oblique vein from the left renal vein (LRV) which joins the third lumbar vein and terminates in the IVC at the level of the third lumbar vertebra. Associated with this, there were three renal arteries (LRA) on the left side.

The CAV ring in Figure 8 is unique in that the dorsal



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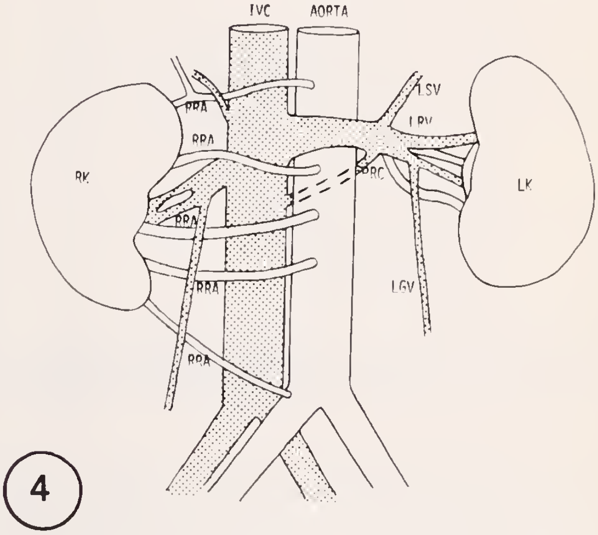

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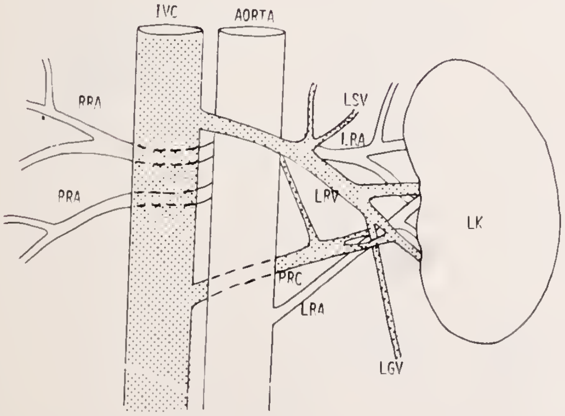
FIG. 3. Shows the angles of termination of the LSV and the LGV in the LRV and distances A and B between the IVC and the LSV and LGV respectively.

FIG. 4. Closed type of circumaortic venous ring.



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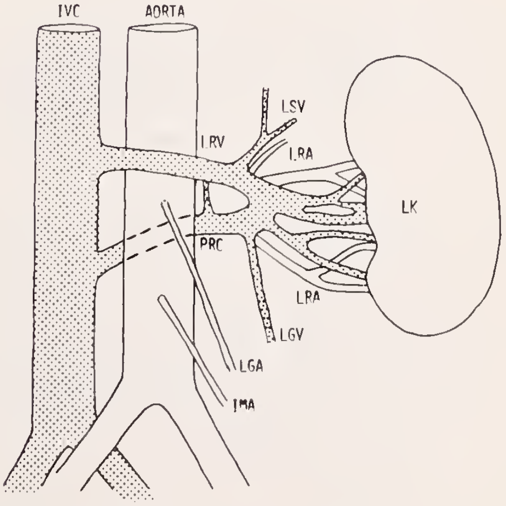

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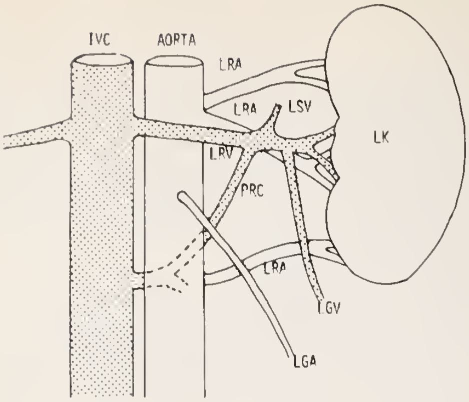
FIG. 5. Open type of circumaortic venous ring.

FIG. 6. The left gonadal vein (LGV) drains into the dorsal limb of the circumaortic ring.



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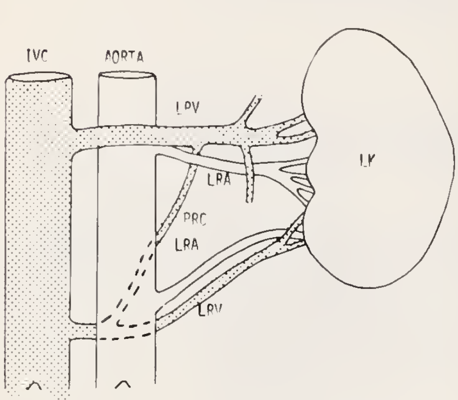

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FIG. 7. Open type of CAV ring. The PRC joining a lumbar vein.

FIG. 8. The retro aortic left renal vein communicating with the preaortic left renal vein by the dorsal limb (PRC) of the renal collar.

limb (PRC) is formed by an oblique vein draining from the ventral limb off the CAV ring into the retroaortic left renal vein (LRV) which seems to drain the lower pole of the left kidney. There were two renal arteries LRA on the left side.

Retro Aortic Left Renal Vein

This anomaly was detected in three cadavers. Out of the three, two were exactly similar and were found in male specimens. In both, the portion of the abdominal aorta ventral to the vein showed an aneurysmal dilation (AD).

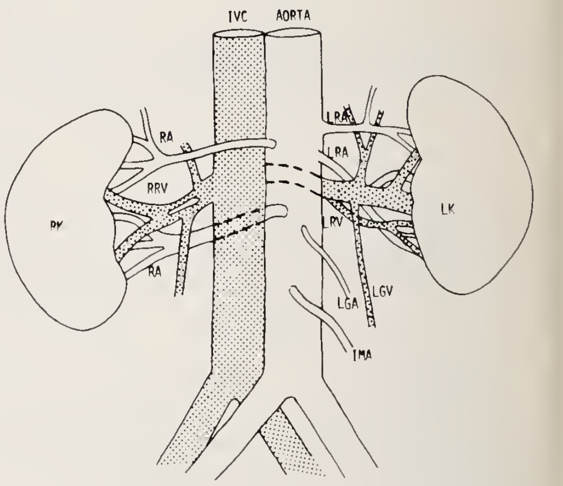
In Figure 9, the preaortic left renal vein is totally absent and the retroaortic vein was present. This retroaortic left renal vein (LRV) was located at the same level as the normal preaortic left renal vein. The right renal vein (RRV) was normal. The left suprarenal and the left gonadal veins drained into the retroaortic left renal vein. There were two renal arteries (LRA) on the left side and an circumvenous ring was formed on the right side by two renal arteries (RRA).

In Figure 10, the left renal vein (LRV) emanated from the hilum of the left kidney and pursued an oblique course downward towards the abdominal aorta, passed behind the aorta, and divided into two tributaries that drain separately into the IVC. The lower retroaortic tributary was 7 cms below the termination of the right renalvein. The left renal vein received the left suprarenal and the left gonadal vein. The abdominal aorta ventral to the retro aortic portion of the left renal vein showed an aneurysmal dilation (AD).

Double IVC. In one cadaver, there was a vein from the left common iliac vein draining into the left renal vein. This vein was about the same size as the IVC on the right side. The left suprarenal and the left gonadal veins drained into the left renal vein.

Discussion

In 88% of the cadavers, the left renal vein was preaortic in position. Since the primitive suprarenal vein drained into the intersubcardinal anastomosis and the left gonadal vein drained into the lateral portion of the renal collar, the developed left suprarenal vein almost always



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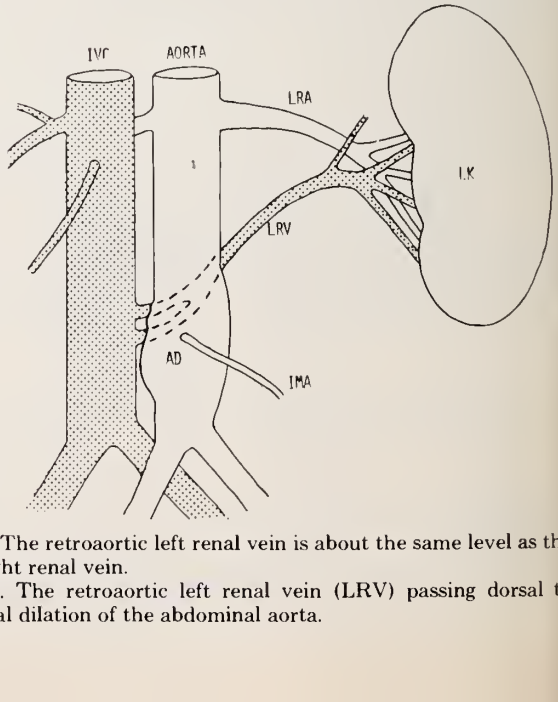

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FIG. 9. The retroaortic left renal vein is about the same level as the normal right renal vein.

FIG. 10. The retroaortic left renal vein (LRV) passing dorsal to aneurysmal dilation of the abdominal aorta.

terminated caval to the termination of the left gonadal vein in the left renal vein. Though ligation of the left renal vein in the dog causes elevation of blood pressure with renal congestion (5), in man, because of the multiple collateral venous pathways, ligation or thrombosis of the vein does not impair the venous drainage or functions of the left kidney (6).

Since the fifties, the left renal vein has been an extremely important landmark for vascular surgeons and urologists. Improvements in surgical techniques involved a more detailed study of the normal and the variations of the venous drainage of the left kidney. The incidence of the circumaortic venous ring varies from 6%–17% (3, 4, 7). In this study the incidence was 8%. According to Mclure and Butler (1) the circumaortic ring is the result of the persistence of the dorsal part of the renal collar formed by the intersupracardinal anastomosis and by the persistence of the lateral part of the collar which is formed by the supra-subcardinal anastomosis. The persistence of the dorsal portion of the renal collar after the disappearance of the ventral portion constitutes a solitary retroaortic left renal vein. The incidence of this anomaly was about 3% in this study.

Based on the distance between the points of termination of the pre- and retroaortic limbs of the CAV ring in the IVC, a closed and an open type of CAV ring could be distinguished. In the closed type (Figs. 4, 6) the retroaortic component is thin and slender and its termination is close to the termination of the preaortic limb in the IVC. In the open type (Figs. 5, 7, 8) the retroaortic component is fairly substantial and terminates in the IVC much lower. Prior knowledge of these variations would be of value in preoperative catheterization of the left renal vein.

By virtue of its position, the retroaortic component of the CAV ring or a solitary retroaortic vein is vulnerable in pathologic conditions affecting the abdominal aorta and the vertebral column. The anatomy of this condition was very lucidly exemplified in the two cadavers (Male) that showed an aneurysmal dilation (AD) of the abdominal aorta above its bifurcation with a compression of the retroaortic left renal vein (Fig. 10). Preoperative nonrecognition of this anomaly could lead to inadvertent trauma to the vein with disastrous consequences (2). Lord et al (8) describe a patient with a fistula between the retroaortic left renal vein and an aneurysm of the abdominal aorta with a clinical picture quite different from that of an aortocaval fistula. Horan and Sharp described a similar case but with a slightly different symptomatology (9). In a series of 20 patients with retroaortic left renal vein, nine veins were injured during surgery and two patients died because hemorrhage and eventual bilateral renal vein thrombosis (10). The retroaortic vein precludes the use of the left kidney for transplantation and for splenorenal shunts (11) because of the difficulty in mobilization. On the contrary, the presence of a circumaortic venous ring might not be detrimental for transplantation even though it would involve recognition and ligation of the retroaortic limb of the ring. Though there is little mention in the literature concerning the disposition of the renal arteries associated with these anomalies, it was found in this study that these venous anomalies are always associated with multiple renal arteries. The presence of a retroaortic left renal vein allows for an easier exposure of the renal arteries and also facilitiates aorticorenal bypass procedure.

Lack of knowledge of the retroaortic and circumaortic left renal vein anomalies during the performance of renal or adrenal angiography could result in false and hazardous results. These anomalies have been blamed for failure or adrenal vein catheterization and could give false values for renin in blood samples obtained from the distal portions of the left renal vein (12, 13). Interpretation of left renal angiograms should take into consideration the existence of these anomalies, because the obliquity of the retroaortic left renal vein might simulate a displacement by a tumour mass.

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Intramural Duodenal Hematoma Mimicking Carcinoma of the Head of the Pancreas

JEFFREY S. FREED, M.D., GILBERT ROC, M.D.*, AND PINKUS H. SZUCHMACHER, M.D., F.A.C.S.

Abstract

Intramural hematoma of the duodenum is often an enigmatic diagnosis. Even with a classic presentation, the diagnosis is often difficult. A patient with a unique presentation of this condition is described. The clinical, radiographic and endoscopic findings mimicked carcinoma of the head of the pancreas. The etiology, pathogenesis, clinical features and management are briefly reviewed.

Intramural hematoma of the duodenum is an enigmatic diagnostic problem with a myriad of presentations. We have encountered a patient with signs and symptoms compatible with carcinoma of the pancreatic head, and only at laparotomy could the diagnosis be established.

Since McLauchlan (1) reported the first case in 1838, 179 cases have been reported in the world literature. We have reviewed the reported cases and added this unusual case of our own.

Case Report

A 62-year-old black male was admitted on May 23, 1977 to St. John's Episcopal Hospital with a complaint of upper abdominal fullness of several days duration. Two days prior to admission he had several episodes of vomiting and low grade fever. There was no history of recent alcohol intake, food intolerance or trauma. There was a recent ten-pound weight loss. The patient was a diabetic on NPH insulin for two years.

Physical examination revealed a well-developed, well-nourished male. Vital signs included: blood pressure 120/80, pulse rate 90/minute, temp. 100°F., respiration 20/minute. There was trace scleral icterus. The abdomen was soft, and a nontender palpable mass filling the epigastrium was identified. Rectal examination revealed no masses or blood. Stools were guaiac positive. The patient had a nasogastric tube inserted with initial drainage of 2000 ml. of nonbilious fluid. Hemoglobin was 16.1 g percent, white blood count 9500; electrolytes within normal limits; blood urea nitrogen 10 mg percent; serum glucose 190 mg percent, direct 1.4 mg percent; alkaline phosphatase 120 units; LDH 280 units; SGOT and PT normal. Bleeding and clotting profiles were normal.

An upper gastrointestinal series demonstrated partial gastric outlet obstruction with a constricting lesion of the duodenum (Fig. 1). A gastroduodenoscopy revealed induration and thickening of the duodenal folds with some fixation of the duodenal sweep.

With a diagnosis of carcinoma of the pancreatic head, an exploratory laparotomy was performed. A large retroperitoneal hematoma involving the entire duodenum and surrounding the aorta was found, the etiology not initially being identifiable. The aorta was examined without evidence of an aneurysm. The hematoma overlying the aorta was opened. With further dissection, the actual diagnosis of intramural duodenal hematoma was made, extending from the second portion of the duodenum to the Ligament of Treitz. Approximately 800 cc of clot was evacuated. Because of the extensive dissection of the duodenum and concern for its viability, a distal gastrectomy, anticolic Billroth II gastrojejunostomy, tube duodenostomy, and gastrostomy were performed.

Postoperatively, the patient had a stormy course with a duodenal fistula that closed after three weeks on intravenous hyperalimentation. All laboratory values returned to normal. A gastrointestinal series revealed a patent anastomosis and a normal duodenal sweep (Fig. 2).

From the Departments of Surgery, *St. John's Episcopal Hospital, Brooklyn, and Mount Sinai School of Medicine of The City of New York, New York, N. Y.

Requests for Reprints should be sent to Jeffrey S. Freed, M.D., Director of Surgery, Long Beach Memorial Hospital, 455 E. Bay Drive, Long Beach, N.Y. 11561.

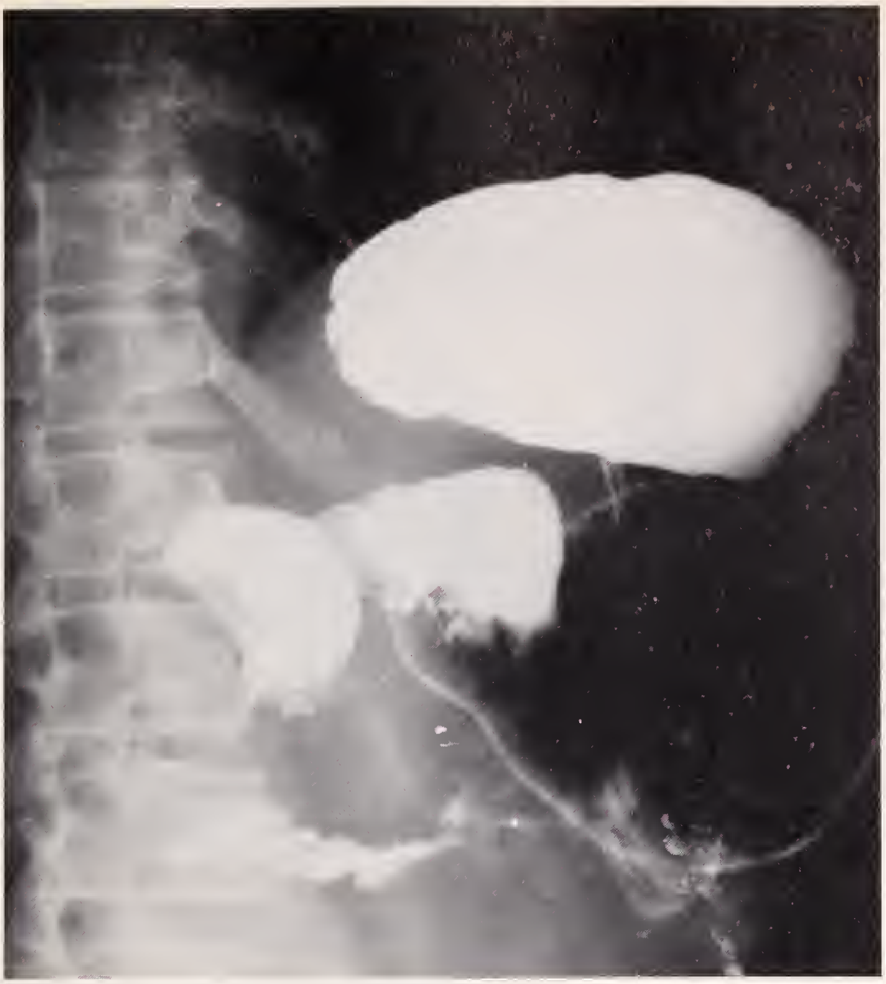

Fig. 1

Discussion

The duodenum in its primarily retroperitoneal position is infrequently traumatized. However, it is the site of more than 50 percent of the intramural hematoma of the small intestine, males being affected four times as often as females (2). Blunt trauma is the most common inciting factor, present in nearly 80 percent of the cases (3). The traumatic incident may be so minor as to be forgotten by the patient. In children it is obvious why it is difficult to obtain a history of trauma, although duodenal hematoma are seen relatively more often in this age group (4).

There are other factors that contribute: anticoagulants (5), blood dyscrasias (6), alcoholism, and pancreatic disease (7). Other rare causes include severe hiccoughs, ruptured aortic aneurysm (8), reduplication of the alimentary canal, duodenal ulcer with hemorrhage (9), Henoch-Schoenlein purpura (10), mucosal intestinal biopsy and pyloroplasty (12).

The case described is unique in its appearance as a spontaneous duodenal hematoma mimicking carcinoma of the head of the pancreas. Clearly, no precipitating cause could be identified in the history, preoperative evaluation or intraoperative findings. Rarely is icterus present with this condition, being reported in only six percent of the collected cases (13, 14). In reviewing the literature, no report of this clinical picture could be found. Scheflan et al did report a case of a ruptured pancreaticoduodenal artery aneurysm masquerading as a carcinoma of the head of the pancreas (15).

Our case illustrates one of the most striking features of an intramural duodenal hematoma. Visible abdominal injury is usually absent and the intramural hematoma is usually an isolated injury. These points made the preoperative diagnosis impossible. The laboratory, radiographic and endoscopic findings were consistent with invasive carcinoma of the pancreatic head. The classical subacute symptom of vague abdominal pain and tenderness associated with signs of high intestinal obstruction with bilious vomiting did not exist in this case. The findings of an epigastric mass, painless jaundice with obstructive chemistries, radiographic evidence of a mass lesion involving the duodenal sweep and endoscopy re-

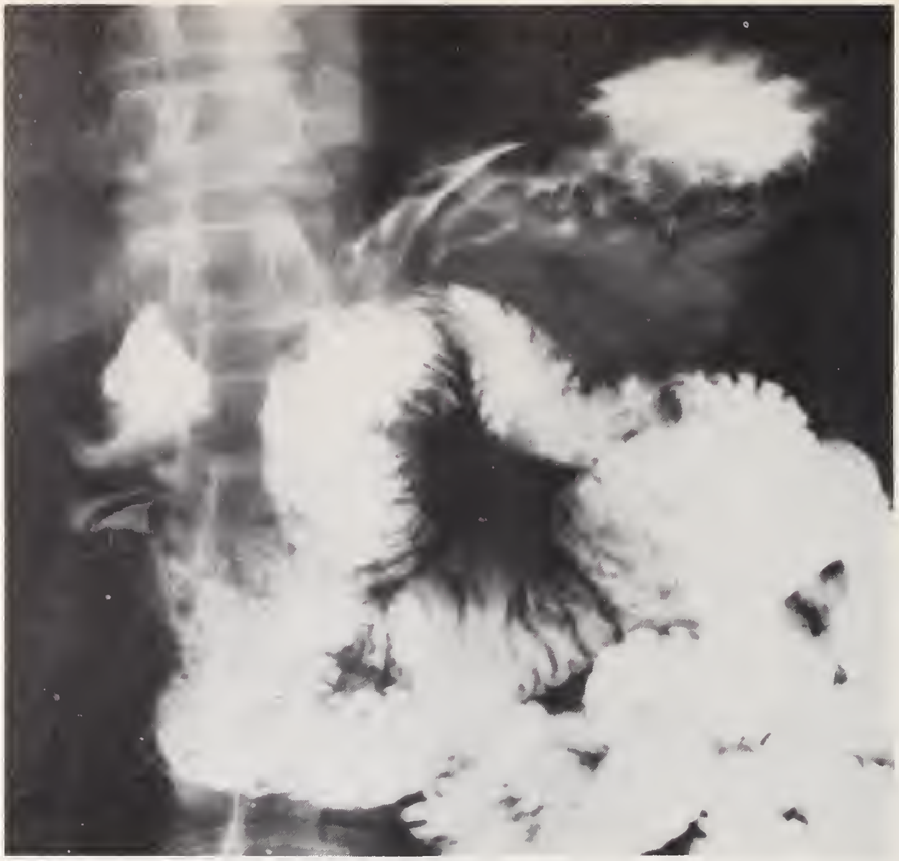

Fig. 2

vealing thickening of the duodenal folds led to a diagnosis of pancreatic carcinoma.

Duodenal hematoma can usually be divided into two types. The first is more common in patients with coagulopathies and involves interstitial bruising of the duodenum wall. A contrast study reveals the "coiled spring" or "stacked coin" appearance described by Felson and Levin (16). The prognosis of this type of hematoma is excellent with nonoperative therapy and support alone.

The second type, which more closely resembles our case, follows tangential forces being applied to the duodenum creating a separation between the mucosa and muscularis, or muscularis and serosa and filling the space with hematoma from the ruptured submucosal vascular plexus. The forces are applied primarily to the convex border of the second portion of the duodenum, causing eccentric narrowing of the sweep on barium x-ray.

Much controversy exists over the management of the second type of intramural duodenal hematoma. Recommendations for operative as well as nonoperative therapy still appear in the literature (17, 18). However, a selective approach is certainly the best in this condition. Conservative therapy is advised in patients with a secure diagnosis of intramural duodenal hematoma in whom no additional injuries requiring laparotomy are identifiable (18). Most patients will resolve within one week with nasogastic suction and intravenous fluids. Lack of enthusiasm for operative therapy results from the difficulties reported in evacuation of these hematomata with diffuse infiltrating hemorrhage and loculations in the bowel wall. The addition of gastrojejunostomy has been advocated at the time of laparotomy, but dysfunction has been described and most authors avoid this additional procedure (20).

In a case with features of the one reported, where the diagnosis is in doubt and relief does not occur with conservative therapy, laparotomy is indicated. Ideally simple evacuation will suffice. If this cannot be accomplished a gastrointestinal bypass may be necessary. If there is injury to the duodenal wall or if viability is in question, complete diversion is essential. With a selective approach to this problem, the majority of patients will not undergo surgery, and the remainder will have procedures that will be to their benefit.

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Rehabilitative Management in Arthritis and Related Disorders

MIRIAM E. LANE, M.D. AND JAMES T. DEMOPOULOS, M.D.

Abstract

This review article details the three main components of rehabilitative management in arthritis: functional evaluation, goa setting and rehabilitative treatment. A functional assessment system for musculoskeletal disability developed by the authors is described. Current therapeutic methods and techniques are discussed, as they pertain to pain management, prevention and correction of deformity, increase in mobility and self-sufficiency and psychosocial and vocational adjustment. The role of the physiatrist in team management is emphasized.

The term arthritis, which literally means joint inflammation, is applied to a multitude of diseases of the musculoskeletal system, ranging from localized, relatively benign conditions such as bursitis and tendinitis to major polyarticular disability states, such as osteoarthritis and rheumatoid arthritis; the latter has both articular and extraarticular manifestations. Rehabilitative management in these conditions is perhaps the classical example of the combined clinical application of both components of physical medicine and rehabilitation.

The therapeutic use of physical agents, such as heat and water, in the treatment of musculoskeletal disorders goes back to ancient times. The modern concept of restoring the physically disabled patient to optimum functional capacity and psychosocial and vocational adjustment is more recent. Whereas, the local application of therapeutic physical modalities, including therapeutic exercise, will usually be beneficial in localized disease, the treatment of progressive musculoskeletal disability involves the additional dimensions of disability evaluation and team management.

It has been estimated by the Arthritis Foundation that about 10% of the world's population have arthritic conditions. In the United States, some 20 million people require medical care and, of these, 3.5 million are significantly disabled (1). Musculoskeletal complaints were found to be the second most frequent reason for ambulatory patients to seek medical care (2). This study also showed that four of the five groups of chronic conditions that most often lead to disability involve the musculoskeletal system. However, when comparing the effects of various diseases on the population's health, it is necessary to consider the duration of illness. Rheumatic disease and injuries afflict a younger population and, therefore, contribute more patient years of disability.

The economic impact of chronic disease can be expressed in direct and indirect costs, according to Rice (3). This concept was studied by R. Meenan et al on a sample of 50 patients with rheumatoid arthritis (RA), stage III (4). Direct medical costs in this group were three times the national average. Indirect costs caused by lose of income were at least three times higher than the medical costs. Psychosocial costs, a component of indirect costs of illness that is hard to quantify, were experienced by more than half of the patients in this group and consisted of marital breakup, changes in family structure of employment as well as psychotic disturbances. Although 58% of the direct medical costs was covered by insurance, only 42% of lost income was covered by transfer payments. These uncovered indirect costs are the greatest economic burden for patients with advanced chronic RA.

These data on high prevalence, long duration of illness and high economic impact of arthritis-related disability have important practical implications for rehabilitative management. The high demand for treatment resources exceeds their availability, especially for long-term treatment courses in chronic cases. Thus, long-term treatment planning must make provisions for home treatment methods. Treatment in the hospital setting–in or outpatient–should be planned with a time frame in mind. The discrepancy between demand and availability of treatment resources also underlines the necessity for rigorous evaluation criteria as a basis for treatment planning.

From the Department of Rehabilitation Medicine, Hospital for Joint Diseases and Medical Center, New York, N.Y.

Requests for reprints should be sent to Miriam E. Lane, M.D., 301 East 17th Street, New York, N.Y. 10003.

Therefore, a comprehensive functional evaluation is the initial component of rehabilitative management, to be followed by goal setting and rehabilitation treatment.

Comprehensive Evaluation

In the field of arthritis and related disorders, evaluation systems are being developed in rheumatology, orthopaedics and rehabilitation medicine, consisting of functional tests and measurements. The basic concepts involved in the development of such evaluation systems are: economy (ease of performance); validity (the measurement really measures the parameter it is supposed to); objectivity (interobserver agreement on the measurement); reliability and repeatability (agreement between test and retest); and sensitivity (responsiveness of the test to alterations in the observed object) (5).

Evaluation systems (ES) in rheumatology (6–12) are disease oriented and are predominantly indices of clinical activity in rheumatoid arthritis. Multiple Orthopaedic ESs have been developed, geared primarily to specific surgical procedures. These systems will usually include physical functional parameters, such as range of motion, ambulation status, deformity, etc.; but in most cases, these will address the specific joint under study.

Evaluation systems in rehabilitation medicine initially dealt with general disability evaluation, concerning the physically disabled patient, regardless of etiology (13–15). The emphasis then shifted toward evaluation of rehabilitation outcome (16–19). In the field of polyarticular disability, Covery and Minteer (20) developed a system of functional assessment containing 19 items relating to ADL and mobility skills.

We have developed an evaluation system based on twenty functional variables, selected from the major areas of rehabilitation (medical, physical, psychological, social, and vocational) (21, 22). All physical and medical variables are patient related (pain, range of motion, muscle strength, ambulation status, cardiovascular status, surgical complications, etc.). The psychosocial and vocational variables include parameters such as family situation, means of support, and living environment, in addition to patient-related factors (depression, motivation, work history, etc.). Each variable is graded numerically 1–5, with lower values representing closer to normal function. The resulting unweighted scores are added into one aggregate total functional score (TFS) with possible ranges from 20–100. This TFS is determined on admission, discharge and one-year follow-up. Through these serial assessments, the system monitors the efficacy of the rehabilitation program. The more complex disability will generally score between 40–80 on admission. An improvement of 10–20 score points is to be expected on discharge, especially in postsurgical cases, expressed mainly in the physical and medical parameters. The follow up will reflect the maintenance of these physical gains, as well as improved psychosocial and vocational adjustment.

Goal Setting

Goal Setting is the next step in rehabilitative management. It is based on evaluation results and team input from both the multidisciplinary medical team and the rehabilitation team involved in the patient's care. The physiatrist plays a dual and pivotal role in team management. As a member of the multidisciplinary medical team, he works together with the primary care physician and/or rheumatologist, as well as the orthopaedic surgeon in the establishment of the overall treatment goals. As the leading professional of the rehabilitative team, the specific methodology for the attainment of these goals is developed and implemented through team input and consultation with all members.

General rehabilitation goals for the patient with musculoskeletal disability include: decrease of pain, prevention and correction of deformity, increase in mobility and selfsufficiency, psychosocial and vocational adjustment.

Rehabilitative Treatment

Rehabilitative treatment seeks the attainment of these goals. Rehabilitative treatment is problem oriented and is an integral part of the total medical management, whether conservative or postsurgical.

Pain Management

The modern management of pain is a multidisciplinary effort involving medical, psychological, physical and surgical approaches. The traditional physical modalities used in the conservative treatment of pain are therapeutic heat and cold. The physiologic effects of local heating are an increased metabolic rate, analgesia, and sedation. The latter two are probably not directly attributable to the increase in local metabolic rate. According to Lehman (23) application of heat to a peripheral nerve causes an increase in the pain threshold in the area of distribution. Heating of tissues has also been shown to affect the gamma fiber activity in muscle (24). The resulting increase in the sensitivity of the muscle spindle to stretch as well as reflexes triggered through temperature receptors may explain the relaxation of muscle spasm following the use of heat.

The physical sources of therapeutic heat are: water, paraffin, electrical energy (simple electrical pad or high frequency currents in shortwave diathermy), spectral energy (infra-red radiation, microwave radiation), and ultrasound. Depth of Penetration: The application of water, paraffin, electrical heating pad and infra-red radiation results in the heating of the superficial tissues. Short-waves penetrate to the subcutaneous tissues and superficial muscle layers, as well as superficially located joints. Microwaves and ultrasound waves penetrate into the deep laying joints. The most frequently used methods of local heating are hot packs or hydrocollators. Paraffin baths are used most often to heat hands and wrists. Ultrasound is of established value in joint contractures resulting from scarring and tightness of the periarticular structures and capsular tissues. Local heating, whether superficial or deep, is beneficial in chronic musculoskeletal pain.

Thereapeutic cold is indicated in acute pain states, especially posttrauma. The stiffness of rheumatoid arthritis is usually aggravated by cooling. Reflex muscle spasm secondary to pain may respond well to cold, for example, torticollis. Therapeutic cold is applied by: immersion (cold water to which ice is added), cold packs or ice massage (immersion followed by rubbing with ice). Hayden and Grant (25, 26) recommend that ice massage be followed by active exercises for best results. This combined method is called cryokinetics.

The use of physical modalities in the management of pain includes transcutaneous electrical neural stimulation (TENS). The method is based on the gate control theory proposed by Melzack and Wall (27) and on the concept that selective stimulation of cutaneous afferent fibers of large diameter will inhibit pain. More than 20 firms in the United States now market TENS devices, including portable models. All TENS devices are solid-state generators that produce pulsed direct current of low voltage and amperage. The current is used to produce electroanalgesia by differential sensory nerve excitation.

Prevention and Correction of Deformity

This is an area of close cooperation between orthopaedics and rehabilitation medicine and is accomplished through orthotic management (bracing, splinting), therapeutic exercise, and corrective surgery.

Lower extremity orthoses currently in use have evolved, in part, from applications of prosthetic technology. Thus, the patellar weight-bearing orthosis brace (PTB brace) is based on prosthetic principles of weight-bearing redistribution. This brace provides weight-bearing relief for the ankle-foot complex, while enabling the patient to be ambulatory. Corrective orthoses (three-way knee stabilizer or TKS brace, etc.) are based on the "three-point pressure" principle (two forces in the desired direction, one counter force). These braces are useful in the correction of mediolateral knee instability and are often used in conjunction with surgical correction of valgus or varus deformities.

In the upper extremities static and dynamic splints are used for prevention and correction of wrist and hand deformities. Static splints are designed to keep the joints in functional position whereas dynamic splints are designed to assist desired motion and counteract painful motion. A specially designed, dynamic splint is used in the postoperative period following metacarpophalangeal joint replacement (Swanson prosthesis). The splint assists MCP extension, while at the same time counteracting the pull of the long finger flexors and intrinsics (28). Therapeutic exercises (range of motion as well as strengthening exercises) complement the conservative management of deformity.

Improvement in Mobility and Self-sufficiency

This important rehabilitation goal is accomplished through a judicious combination of physical and occupational therapy techniques such as therapeutic exercise, ambulation training, instruction in activities of daily living and functional activities.

Improvement in range of motion (ROM) is accomplished through specific exercises and hydrotherapy. Range of motion exercises may be passive (done by the physical therapist (PT)), active-assistive (started by the patient and completed by the PT) and active (done by the patient through the full ROM). Active-assistive and active ROM exercises are the preferred types of exercises in postsurgical cases. ROM exercises may be started in the gravity eliminated position (for example Codman's pendulum exercises). Certain ROM exercises are specifically contraindicated following specific procedures. For example, avoiding hip abduction and adduction in the first six weeks following the Charnley LFA, allows the healing of the distal displacement of the trochanter performed during the arthroplasty (29). Shoulder abduction and external rotation are contraindicated following the Neer prosthetic replacement of the shoulder (30).

Hydrotherapy is based on the physical principle of buoyancy according to Archimedes law and is an ideal means of performing ROM exercises in joints that are painfully restricted. Whirlpool baths are used for underwater ROM exercises of the ankle-foot, as well as, wrist-hand complex. The Hubbard Tank provides total immersion and is best suited for the treatment of polyarticular involvement, especially in RA. The therapeutic pool provides the additional possibility of pool ambulation, particularly useful in cases of limited weight bearing.

Balneotherapy or Spa's is a form of general hydrotherapy very popular in Europe, for centuries. In addition to the physical properties of water, certain mineral constituents (sulfur, iodine) as well as the warm temperature (thermal baths) supposedly contribute to the beneficial effect.

Improvement in muscle strength is accomplished by two types of exercises: isometric exercises, consisting of muscle contraction without shortening and, isotonic exercises–contraction with shortening. Isometric exercises are based on the theory that tension is the primary stimulus leading to increased strength, whereas isotonic exercises are based on the theory that power (defined as work per unit/time) is the primary stimulus. De Lorme (31) developed the system of progressive resistive exercise (PRE) in which muscle contractions are obtained against resistance, which is increased in progressive increments of weights.

The start of a muscle strengthening program presupposes a muscle strength in the fair range (able to move through the ROM against gravity). Manual resistive exercises are performed first, progressing to PRE. Muscle groups to be included are the antigravity muscles (quadriceps, hip extensors and abductors) and the so-called crutch-walking muscles (shoulder depressors, elbow extensors, wrist dorsiflexors and finger flexors). In addition, specific muscle groups will be strengthened, based on the individual evaluation of the patient, diagnosis and disability.

Functional activities in occupational therapy will complement the exercise program. They are geared to emphasize the use of specific muscle groups of the upper extremities, for example, shoulder abductors and external rotators in "frozen shoulder" or forearm supinators, wrist dorsiflexors and finger flexors following Colles' fracture. In addition to increase in muscle strength, functional activity will improve endurance, coordination and dexterity.

Ambulation training in musculoskeletal disabilities takes into consideration the indicated restrictions in weight bearing as well as polyarticular involvement. During normal gait, the hip joint bears weights roughly equal to three times the body weight, (gravity, abduction mechanism supporting upright position against medial pull of gravity, flexor-extension mechanism supporting upright position against forward or backward pull). The use of crutches will subtract about two body weights; the use of a cane on the opposite site will subtract one body weight. Forces in excess of gravity are placed through the knee joint, especially in stair climbing when the body weight is propelled upwards by a powerful contraction of the quadriceps to extend the knee and lift the body. These problems are compounded in the patient with joint pathology, muscle weakness and limited ROM of the upper extremities, requiring special adaptations of gait assistant devices, such as platform crutches, etc. Pool ambulation is an ideal way to initiate partial weight bearing ambulation. Ambulation training proceeds on level surfaces, and elevated surfaces. The capability to negotiate stairs and use public transportation will be a determining factor in later vocational adjustment.

Training in activities of daily living (ADL) is geared toward improvement in self sufficiency. Numerous self-help devices are available to assist the patient in dressing, feeding and toilet activities. Home needs are evaluated prior to discharge and raised toilet seats, grab bars, nonskid bath mats and other assistive devices will be prescribed.

Psychosocial and Vocational Adjustment

Psychosocial and vocational adjustment represents a complex interface between medical, psychological, social and economic factors related to the patient, his family, the community and society as a whole. This is not necessarily related to the extent of physical disability. A severely disabled arthritic may have a satisfying and productive life; whereas, a mildly involved patient may be so emotionally crippled that he is unable to function in society. The relationship between psychological factors and musculoskeletal symptoms is apparent in several clinical situations. Thus, in pure psychogenic rheumatism, musculoskeletal symptoms are thought to be a response to emotional problems without the contribution of organic disease. In superimposed psychogenic rheumatism, additional symptoms without constitutional validity are superimposed on actual arthritis. In residual psychogenic rheumatism, symptoms persist because of emotional stresses rather than organic sources (32). The fundamental psychological responses to advanced polyarticular disability are similar to those observed in other chronic diseases, consisting of anxiety, dependency, anger and loss of gratification (33). These emotional factors condition the patient's reaction to his disease, family, and social environment. A supportive family setting will greatly enhance the patient's adjustment. The achievement of ADL independence will have an important positive effect on the patient's interpersonal relationships at home. However, full social adjustment implies the capacity for external social and cultural activities. In this context, the problem of housing and of architectural accessibility for the physically disabled is receiving better recognition, but much remains yet to be done.

Vocational adjustment is a job placement consistent with the physical and industrial potential of the patient. In addition to patient-related factors (motivation, educational level, previous work history, etc.) and to the availability of full structured vocational rehabilitation programs, general economic conditions play a very important role in job placement. The most difficult resettlement problems involve patients whose jobs required heavy physical labor, especially if they lack sufficient education to be retrained for less physically demanding work. The unskilled, short-term employee is at a particular disadvantage in times of increased unemployment. Professionals and highly skilled office workers have the best chance of satisfactory resettlement.

Members of the rehabilitation team (psychologist, social worker, vocational counselor) are involved in the process of psychosocial and vocational adjustment through supportive counseling of the patient and his family, vocational testing and referral for retraining, as needed. Members of the rehabilitation team work in cooperation with community resources, as well as state and federal agencies towards the attainment of maximal adjustment.

Rehabilitation management in arthritis and related disorders is an ongoing process. The most challenging problems are faced in the management of patients with advanced polyarticular disability. The development of modern rehabilitative concepts and techniques has benefited from and paralleled the progress in medical and surgical methods of treatment over the past 30 years. The advent of total joint replacement surgery has greatly improved the functional outlook for the severely disabled patients.

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Halothane, Autoimmune Diseases and the Liver

VASILIOS PRATILAS, M.D., MARGARET A. PRATILA, M.D., AND HARRY SMITH, JR., PH.D.*

A decreased latent period and the frequent incidence of jaundice after repeat halothane anesthesia have caused some authors to propose the possible presence of an accelerated immunologic process (1). Recently it has been suggested that subjects prone to develop organ-specific autoimmunity might also develop hepatitis following halothane anesthesia (2).

Certain clinical disorders, namely myasthenia gravis, Hashimoto's thyroiditis, systemic lupus erythematosus, ulcerative colitis, Crohn's disease, ankylosing spondylitis, biliary cirrhosis, and chronic active hepatitis are considered as probably immune mediated diseases (3–9).

We present a number of patients with these diseases in which halothane was used. Our aim was to examine if, indeed, subjects with organ-specific autoimmunity had a greater incidence of unexplained hepatitis following halothane or liver dysfunction as evidenced by serum enzyme levels.

Materials and Methods

There were 164 patients in our series (93 males, 71 females), of whom 21 females and 11 males were markedly obese. Autoimmune diseases diagnosed in these patients were: myasthenia gravis (36 patients), Hashimoto's thyroiditis (nine patients), systemic lupus erythematosus (12 patients), ulcerative colitis (37 patients), Crohn's disease (34 patients), ankylosing spondylitis (15 patients), biliary cirrhosis (nine patients), active chronic hepatitis (12 patients). The diagnoses in these patients were made on the basis of history, clinical findings, special histo- and serologic tests, and the response to specific treatment.

Patients with congestive heart failure, who were on cytotoxic drugs or undergoing radiotherapy, on quinidine or aldomet therapy, or who had received a blood transfusion, were excluded from our series. We also excluded patients who were having operations in the upper abdomen.

With the exception of those patients with biliary cirrhosis and chronic active hepatitis, all patients had normal liver chemistries preoperatively. This was indicative of normal hepatocyte function. Anesthesia was administered for surgery that was unrelated to the patient's autoimmune disease.

The criteria used in this study for the effect of halothane on the hepatocyte were the changes in each patient's SGPT level measured at three points in time: Preoperatively, five days postoperatively, and ten days postoperatively. Abnormal SGPT levels are considered by Taylor (10) to be the most specific evidence of hepatocyte injury. All liver enzymes were obtained from the patients' charts. They were ordered by each patient's surgeon for routine postoperative care. Using repeated measures analysis of variance techniques for each group separately, statistical significance tests for SGPT changes were made using the $\alpha = 5\%$ level. In addition, other liver chemistries-CPK, SGOT, serum albumin and bilirubin were noted. Patients' temperature charts were noted with particular attention given to temperature development with no obvious cause and to the development of eosinophilia.

Anesthesia

All patients received diazepam 10 mg and atropine sulfate 0.4 mg intramuscularly, one hour prior to surgery, except for the myasthenic group that received no premedication. Patients in the myasthenia gravis group were given only sodium thiopental 250 mg intraveniously (IV) for induction of anesthesia followed by halothane, in increasing concentrations of 2% or 3%, with oxygen in a semiclosed system. When sufficient depth of anesthesia was achieved, an oral endotracheal tube was inserted. Anesthesia was maintained with halothane 2%–3% in N20/02, 50%/50%. The patients were automatically ventilated.

The remaining patients received sodium thiopental 250 mg IV followed by succinylcholine 60–100 mg for endo-

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From the Departments of Anesthesiology and *Biostatistics, Mount Sinai School of Medicine of The City University of New York, N.Y.

Requests for reprints should be sent to V. Pratilas, M.D., 150 East 69th Street, New York, N.Y. 10021.

TABLE I

SGPT Means ± Standard Error of the Mean for Each Patient Group, Pre-op, 5 Days Post-op, and 10 Days Post-op

	PRE-OP	POST-OP		% OF PTS (with at least 1 SGPT reading post-op > pre-op)
		(5 days)	(10 days)	
Biliary Cirrhosis (n = 9)	161 ± 6.62	162 ± 5.18	147 ± 5.28	4/9 = 44.4%
Chronic Active Hepatitis (n = 12)	277 ± 10.34	283 ± 7.28	272 ± 10.56	7/12 = 58.3%
Systematic Lupis Erythematosus (n = 12)	21 ± 2.97	21 ± 2.36	17 ± 1.72	8/12 = 66.6%
Ankylosing Spondylitis (n = 15)	22 ± 2.58	25 ± 2.97	26 ± 2.55	12/15 = 80.0%
Myasthenia Gravis (n = 36)	24 ± 1.71	26 ± 1.75	24 ± 1.66	23/36 = 63.8%
Hashimoto's Thyroiditis (n = 9)	23 ± 3.45	24 ± 2.89	26 ± 3.19	5/9 = 55.5%
Crohn's Disease (n = 34)	23 ± 1.83	24 ± 1.77	24 ± 1.69	27/34 = 79.4%
Ulcerative Colitis (n = 37)	27 ± 2.01	26 ± 1.75	25 ± 1.74	19/37 = 51.3%

tracheal intubation. Maintenance of anesthesia was with halothane 1%–2% in N20/02, 50%/50%. Muscular relaxation was produced by d-tubo-curare in a total dose of 30–60 mg IV. Automatic ventilation 10/ml/kg/min was started once stabilization had been achieved. Anesthesia time varied from two to six hours. Vital signs remained normal throughout this time or the patient was excluded from the series. Arterial blood gases during anesthesia showed PaO_2s above 110 mmHg and $PaCO_2$s that ranged from 38 to 43 mmHg.

Patients with liver disease (chronic hepatitis or biliary cirrhosis) received halothane for the following reasons:

1. The patient had a history of severe asthma, chronic bronchitis, or severe emphysema with fibrosis. Large doses of morphine or fentanyl have been reported to cause chest rigidity (11) or bronchospasm due to release of histamine (12).
2. The patient had a history of episodes of hepatic failure. Irreversible hepatic failure has followed the use of narcotics in these patients (13). Narcotics require normal liver function for elimination (14).

Results

All patients had an uncomplicated surgical recovery. No patient developed a temperature of unknown cause that could be attributed to halothane. No patient developed significant eosinophilia. The liver enzymes, with minimal fluctuations, remained within normal limits. (Normal SGPT range in our institution = 1–53 mu/ml).

Table I shows the SGPT mean levels ± standard error of the mean levels for each group of patients, preoperatively, five and ten days postoperatively. There were no significant changes ($p > .05$) in SGPT levels in the ten days postoperatively in any of the patient groups. The last column indicates the percentage of patients in each group who had at least one marginal increase in SGPT levels even though not statistically significant.

Discussion

Hepatic necrosis in the postoperative period is rare (15) but may follow the administration of halothane or any other anesthetic agent with virtually the same incidence (16). It is not known whether the initial offending agent is halothane itself, a metabolite or a completely unrelated factor. The pathologic process may be direct dose related toxicity (17), an allergic reaction (1), or some other form of reaction. Even the histologic lesion is not pathognomonic when the technique of blind analysis is used (18).

In our group of patients, diagnosed as having autoimmune disease, who were exposed to halothane we found neither postoperative hepatitis nor elevation of liver enzymes that would indicate the presence of liver dysfunction.

Walton and his colleagues (2) have shown a much greater incidence of liver, kidney microsomal and thyroid antibodies in patients with unexplained hepatitis following halothane, than in patients whose jaundice was related to identifiable factors. They believed that obese women with a tendency to organ-specific autoimmunity might be more at risk in the development of liver dysfunction following halothane use. This has not been evidenced in our group of patients. Those patients who were overweight and female had postoperative enzyme levels that did not differ from the remaining patients. Were the thyroid and liver, kidney microsomal antibodies to be pathognomonic, we would expect the presence of a residual thyroid disease and renal disease in patients with unexplained hepatitis following halothane. This has not been reported.

The coexistence of two or more autoimmune diseases in the same individual has been well documented (19). However, there is no evidence that one autoimmune disease can predispose to, facilitate the development of, or aggravate another autoimmune disease.

Mackay (20) has hypothesized that the coexistence of genes for certain antigens causes a change in balance between proliferation and tolerance responses in specifically stimulated antigen-reactive cells. With the balance moved towards proliferation, individuals with this genetic configuration would be expected to produce a strong immune response. If true, this might explain why only an occasional patient develops unexplained hepatitis following halothane induction.

Van Dyke (21) has shown that under anaerobic conditions there was enhanced binding of reactive halothane intermediates to hepatic proteins and phospholipids in the isolated perfused rat liver. Binding was proportional to the amount of metabolism, which indicated what was binding was a metabolite. Binding was also inversely proportional to the rate of perfusion. These findings of a reductive pathway of halothane biotransformation and covalent binding to microsomal elements imply possible toxicity.

Cohen et al (22) have demonstrated the presence of N-trifluoroacetyl-2-aminoethanol as a urinary metabolite in humans. The most probable source of this metabolite is the binding of the trifluoroacetyl radical, formed by hydroxylation and debrominization of halothane, with phosphatidyl-ethanolamine (a normal lipid constituent within the cell membrane). The presence of ethanolamide and cysteine conjugates of halothane in the urine suggests the presence of reactive intermediates that conjugate to proteins and phospholipids that may give rise to high molecular weight covalently bound substances which have been demonstrated in the liver (23–26). As Cohen has stated, parenterally given trifluoroacetic acid has been shown in the experimental animal to have limited toxicity (27) and has little bearing as its production is intracellular. Trifluoroacetic acid is completely ionized at physiologic pH levels and would not penetrate cellular barriers from outside. It does seem possible that these covalently bound, halothane metabolite and hepatic-protein complexes could stimulate immunogenic responses.

However, Walton et al (28), using samples of blood obtained from patients with unexplained hepatitis following halothane, performed lymphocytic transformation and leucocyte migration tests in the presence of trifluoroacetylated human liver specific protein and trifluoroacetylated human serum albumin. The authors were unable to confirm that cell-mediated immunity contributes to the pathogenesis of unexplained hepatitis following halothane.

Vergani and his co-workers (29) have shown in vitro sensitization (inhibition or stimulation of leucocyte migration) in response to a liver homogenate obtained from rabbits pretreated with halothane in eight of twelve patients with liver dysfunction following halothane. Antigenic material was prepared from rabbit livers in lieu of human livers since they share certain antigenic determinants (30). Sensitization was not observed with either pretreated animal homogenates or in patients who did not develop liver dysfunction following halothane. The authors suggest that the homogenate contained material more closely related to that which generated the immune response in vivo than halothane itself. However, before the relevance of this immune response to the pathogenesis of liver damage can be answered, the site of the antigenic material in the liver cell must be known. It appears more likely that an immune-mediated destruction of the hepatocyte would be induced by an alteration in the antigenicity of the hepatocyte membrane rather than intracellular constituents, since only cell membranes would be accessible to immunologic effective systems in vivo.

An alternate mechanism of hepatic cell destruction has been described by Bradfield and Wells (31). About 15% of the hepatic lobular cells are littoral cells, many of which are phagocytic. These Kupffer cells clear, by phagocytosis biologically dangerous substances from the blood stream (32). This has been shown experimentally in mice, in which clearance of particles from blood into the liver is followed by hepatocyte mitosis that probably indicates regeneration after acute hepatocellular damage (33). Animal studies have also shown that clearance of endotoxin (34) or immune complexes (35) by Kupffer cells from the blood may lead to local release of lysosomal enzymes. Deficiency of normal lysosomal enzyme antagonists would tend to increase this enzymeinduced hepatocellular damage.

Summary

In summary, our findings indicate that no increase in the incidence of hepatocellular damage occurs in patients with autoimmune disease when they are exposed to halothane. We have discussed some of the experimental work and hypotheses explaining possible actions of immune complexes in production of unexplained hepatitis following halothane. The experimental work is contradictory and individual findings often lacking in support by other authors.

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Massive Benign Prostatic Hypertrophy

RAN ABRAHAMY, M.D., HAROLD MITTY, M.D.,* AND HANS E. SCHAPIRA, M.D.

Abstract

A case of giant prostatic hypertrophy weighing 550 grams is presented.

Antegrade pyelogram was performed to rule out a ureteral lesion after unsuccessful retrograde.

The transvesicocapsular approach used for enucleation was found to be satisfactory in regard to exposure, enucleation, and hemostasis.

Introduction

The term massive or giant benign prostatic hypertrophy should apply to any prostate weighing 500 grams and over. Giant prostatic hypertrophy, because of the gland's size, can present diagnostic as well as management problems. Nine cases of massive prostatic hypertrophy have been reported and we would like to add one more case to emphasize the following points.

1. The transvesicocapsular approach chosen for this massive prostatic enlargement gave an excellent exposure for enucleation and hemostasis.
2. The hemostasis within the prostatic fossa was improved by using an over inflated Foley balloon in the immediate postoperative period.
3. Antegrade pyelography is indicated when a retrograde study cannot be done, which is often the case in massive prostatic enlargement.

Case Report

An 84-year-old white male was admitted for work-up of total gross painless hematuria. For the last ten years, he complained of a progressive decrease of the urinary stream, diurnal frequency every two hours, nocturia X 5, sensation of incomplete voiding, urgency and terminal dribbling. Marked constipation was present for the same period of time. Pertinent findings on physical examination were a mass in the suprapubic area persisting after urethral catheterization and massive enlargement of the prostate which felt benign on rectal palpation. The upper border of the gland was beyond finger's reach. Complete blood count and blood chemistry studies were within normal limits.

An excretory urogram revealed prompt bilateral function and mild dilatation of the right ureter with nonvisualization of its distal third. There was also marked elevation of the bladder base and a small right bladder diverticulum (Fig. 1). Cystopanendoscopy with an attempt of right retrograde was unsuccessful. Only the tip of the instrument could reach the bladder and the ureteral orifice could not be visualized. A right percutaneous antegrade pyelogram was performed (Fig. 2) that demonstrated a kink in the right lower ureter without evidence of intrinsic or extrinsic lesion.

An open prostatectomy was performed. Because of the massive hypertrophy a transvesicocapsular approach was chosen. Two enormous lateral lobes and several small adenomas weighing 30–50 grams were enucleated from the prostatic fossa which was larger than the empty bladder. The specimen weighed 550 grams. A #20 pear shaped, fluted two-way catheter with a 75 cc balloon inflated with 250 cc of sterile water was placed in the prostatic fossa. A #30 Malecot catheter was placed for suprapubic drainage. The patient required two units of blood in the operating room and three more units during the postoperative period. The Foley balloon was deflated gradually. The suprapubic tube was removed on the ninth postoperative day and the Foley catheter was removed on the 12th postoperative day, the patient voiding with a good stream and with good control. He was discharged on the 15th postoperative day. The pathology report stated "Extremely large fibroadenomatous prostate weighing 550 grams."

Discussion

The average weight of the hypertrophied prostate gland as reported by Van Buren (1) and by Alcock (2)

From the Departments of Urology and *Radiology, The Mount Sinai Hospital, New York, N.Y.

Requests for reprints should be sent to Dr. Hans E. Schapira, 47 E. 77 St., New York, N.Y. 10021.

varies between 38 and 41 grams. Massive prostatic enlargement above 500 grams is unusual and can at times present diagnostic as well as management difficulties.

Of the nine cases of giant prostatic hypertrophy reported in the literature (3–11), four died and often there was marked bleeding from the prostatic fossa requiring packing and even reexploration. Several communications in the past suggested the transvesicocapsular approach for performing a prostatectomy but it has not received wide acceptance (12–14).

We would like to emphasize that this approach gave an excellent exposure of the prostatic fossa and of the bladder, permitting an easy enucleation as well as meticulous hemostasis within the prostatic fossa and the bladder neck.

As suggested by Middleton (6) in massive prostatic hypertrophy there are many natural cleavage planes between the hyperplastic spheroids and, using those planes, facilitates the enucleation. In the instance of massive prostatic enlargement, the surgical capsule is overstretched and in the immediate postenucleation period probably fails to contract. This flaccid capsule may be responsible for profuse postoperative bleeding. The ability to inflate the 75 cc balloon of the pear-shaped, fluted two-way catheter to the capacity of 250 cc with sterile water, and its placement in the prostatic fossa, added an important factor to the hemostasis in the postoperative period. The balloon was deflated gradually to 40 cc during the first four postoperative days and remained intact.

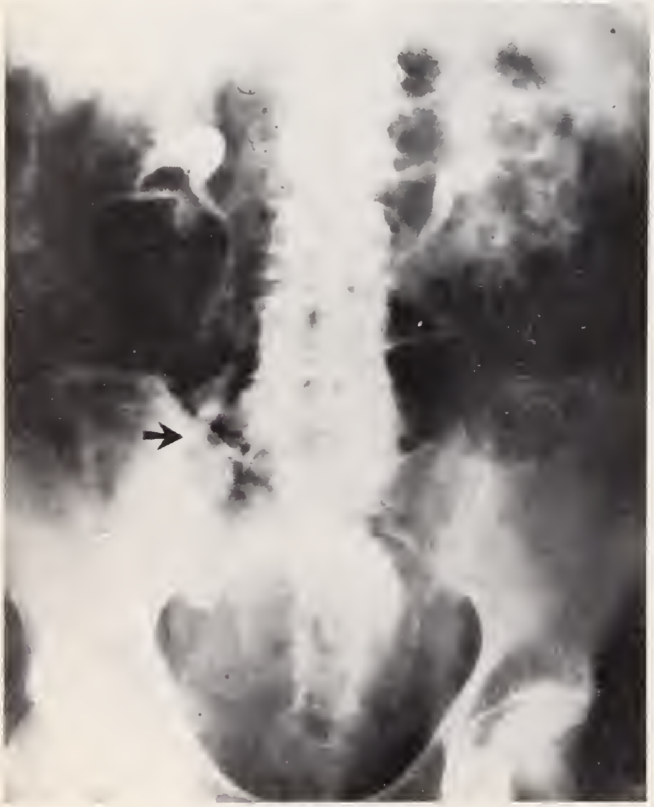

Fig. 1 Excretory urogram demonstrating a large prostatic mass elevating the bladder base. The distal third of the right ureter is not seen (arrow). Small right bladder diverticulum.

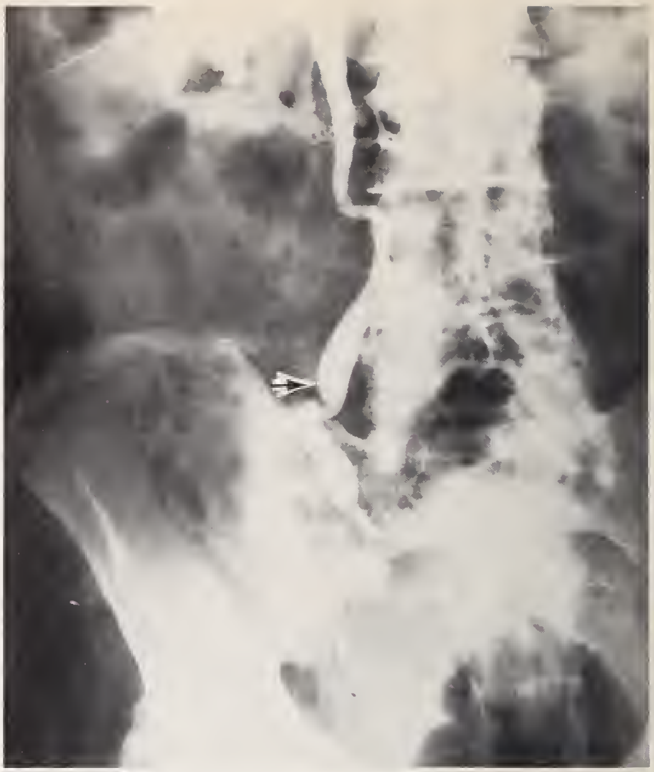

Fig. 2 Antegrade pyelogram demonstrating the area in question of right ureter representing a kink without presence of intrinsic lesion. (arrow)

Often the marked prostatic hypertrophy hides the ureteral orifices from the cystoscopic field of view. An inadequate excretory urogram or one suggesting pathology of the collecting system with unsuccessful retrograde remains one of the absolute indications for antegrade pyelography (15). This diagnostic procedure can be performed with ease and safety using the Chiba or "skinny" needle with guidance by fluoroscopy or ultrasound.

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Hypernephroma at The Mount Sinai Hospital

ARGIL WHEELOCK, M.D. AND MICHAEL CORRIGAN, M.D.

Abstract

Forty-three cases of hypernephroma were reviewed with respect to clinical and laboratory findings. Poor prognostic indicators included elevated serum alkaline phosphatase, hypercalcemia and stage D disease. All stage D patients were dead within two years, regardless of treatment modality.

Case Reports

The symptoms and laboratory findings on admission of forty-three cases of hypernephroma from The Mount Sinai Hospital for the period 1971–1975 were reviewed. The past hospital follow-up was also available in thirty-three of these cases.

Age: Age ranged from 33 to 79 years old. The mean age was 62 years.

Sex: There was a slight predilection toward the male sex with 25 males (60% of the total) and 18 females.

Symptomatology and Physical Findings: Flank pain (30% of the patients), gross hematuria (30% of the patients), and significant weight loss (37% of the patients) were the most common symptoms at the time of admission (Table I).

The most common physical findings were a palpable flank mass (50% of the patients), fever (25% of the patients) and hypertension (16% of the patients).

The classic triad of pain, hematuria and a palpable mass was present in seven percent of the total. Most other series have reported about twice this percentage.

Laboratory Data: Anemia was present in 52% of the male patients and in 39% of the females. No patients had polycythemia in this series but this has been a finding in some recent patients in our hospital.

The sedimentation rate was determined in only sixteen patients and was elevated in 88% of these.

Urinalysis revealed proteinuria in 35% of the patients. Gross hematuria was present in thirteen patients. An additional five patients had microhematuria. Therefore, forty-five percent of the total group had some form of hematuria (1, 2).

Hypercalcemia was detectable in 10% of the patients. Of these four patients, three had pulmonary metastases at the time of admission. The fourth patient was admitted three months postoperatively with extensive bony metastases.

The alkaline phosphatase was elevated in fifty percent (21 of 43) of the patients (Table II). Only one of these patients had abnormal liver chemistries. One half of the patients with elevated alkaline phosphatase had overt metastases (on chest x-ray, bone, or liver scan) during their initial evaluation. Three of four patients with elevated alkaline phosphatase who did have complete metastatic workup and no sign of metastases on initial evaluation died within one year after surgery. This would indicate that they had occult metastases not detected on initial evaluation. Three of the remaining six patients who did not have complete metastatic workups were dead from the primary disease within three years, again indicating probable metastases at the time of initial presentation. Therefore, at least eigthy-one percent of the patients with elevated alkaline phosphatase presumably had metastases (occult or obvious) at initial evaluation.

Radiographic Data: The chest x-rays showed metastatic disease in 40% (13 of 43) of the cases. None of these ever showed any regression.

Bone scans were done in sixteen patients only and 38% of these scans were positive. Five of the six patients with positive scans had elevated serum calcium or alkaline phosphatase while three of ten patients with negative scans had elevations.

Liver scan was performed in thirteen patients. Only

From the Department of Urology, The Mount Sinai Medical Center, New York, N.Y.

Request for reprints should be sent to Argil Wheelock, M.D., 900 Scenic Highway, Lookout Mountain, Tenn. 37350.

TABLE I

Initial Findings	% of Patients
Flank pain	30
Gross hematuria	30
Weight loss	37
Mass	50
Fever	25
Hypertension	16
Anemia	45
Hypercalcemia	10
Alkaline phosphatase elevation	50

TABLE II

Follow-up on 21 Patients with Elevated Alkaline Phosphatase

11 had clinical metastases on initial evaluation and all died within two years.
3 had no clinical metastases on initial evaluation but died within two years with metastases.
3 did not have complete metastatic work-up but died within two years with metastases.
4 lost to follow-up.

two scans were positive and each of these had evidence of metastases elsewhere. These two patients also had elevated alkaline phosphatase. Four of eleven patients with negative scans had elevated alkaline phosphatase.

Renal angiographies were done in thirty-one patients and were considered diagnostic in 90% of these. Four of the thirty-one angiograms showed hypovascularity.

Survival by Stage: The patients were assigned a stage based on the surgical pathology. Stage A disease was limited to renal parenchyma. Stage B tumors involved the renal capsule. Stage C disease included extension into the perinephric fat and/or renal vein. Patients with distant metastases were placed in Stage D.

Two of three patients who had stage A disease were alive for more than three years. One was lost to follow-up.

One of the three patients who had stage B disease died in the early postoperative course of a myocardial infarction. Two were lost to follow-up.

Ten of eighteen patients with stage C disease were dead within three years. Five are known to be alive with postoperative periods ranging from one to seven years. Three were lost to follow-up.

Ten of nineteen patients with stage D disease were dead within six months and all fifteen patients who could be followed were dead within two years. Four patients were lost to follow-up. Nehprectomy had no bearing on the course of stage D patients.

Discussion

The symptoms and physical findings of these patients are typical and agree with the general teachings.

Of the laboratory findings, an elevated alkaline phosphatase seems to be a grim prognostic indicator, whether or not there was other initial evidence of metastatic disease. At least eighty percent of the patients with this finding were dead within three years. Though the follow up on the group with normal alkaline phosphatase is poor, no more than 63% (14 of 22) are dead after three years. These findings would suggest that patients with unexplained elevation of the alkaline phosphatase warrants an intensive metastatic evaluation (3).

Hypercalcemia also offers a grave prognosis as all four patients with this finding were dead within three years.

Stage of the disease determined at the time of evaluation and surgery are helpful in determining prognosis. Stage C patients did very poorly with at least 55% of these patients being dead within three years. All stage D patients who could be followed up were dead within two years and over half of these patients were dead within six months.

Conclusions

Patients with elevated serum alkaline phosphatase and calcium have an extremely poor prognosis. Patients with stage D disease were all dead within two years.

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Too Soon for Marriage
The Need for Experience in Choosing a Career

ARTHUR E. SCHWARTZ M.D. AND JEFFREY D. LIBIN B.A.*

At the beginning of the fourth year of medical school a student typically applies for postgraduate training. This choice essentially constitutes a career decision because it usually also involves a commitment to residency training in a specific field. There is considerable pressure to choose early since the best programs are filled years in advance. A change of mind at a later date is difficult, causing the young physician to lose time and often suffer a sense of failure. The capacity to make the correct choice of career requires maturity, insight and experience which is often beyond that attained by the medical student at this stage of training. Many feel unprepared to make the decision.

In the fourth year the student at Mount Sinai School of Medicine has had less than one year of clinical medicine. This, in general, consists of an exposure to five or six major clinical disciplines with an opportunity for most to spend a month in an elective. The major portion of clinical experience comes in the fourth year–after a career choice has been made. Experience is foreshortened by time limitations but the perception of each discipline may also be altered in subtle ways. Enthusiastic residents and attending staff who devote time and effort to the teaching of medical students will attract them into their specialty. The short exposure makes it possible for the inexperienced student to be dazzled by a charismatic presentation of a discipline without experiencing the reality. Conversely, other fields may suffer from a lack of merchandizing, turning off students to what might have been a rewarding experience.

The choice of a pursuit within medicine is so important that good judgement dictates it be based on first hand knowledge. Since this knowledge must be distilled from the experience provided by the medical school, it is the responsibility of medical educators to offer the developing student sufficient opportunity to acquire the perception and understanding to make a correct choice. This might take the form of seminars offering opportunities to meet with physicians in academic positions, research, and clinical practice. More important would be the chance to spend time informally with these physicians in a day-to-day work setting where first-hand experience could be gained and one-to-one relationships developed. Greater use of electives and preceptor-like arrangements might serve as vehicles for these contacts with the real medical world. Still, such measures seem woefully inadequate to the magnitude of the need.

The classic, wide-ranging internship of previous years had been a faithful guide to generations of emerging physicians, offering a plateau of clinical experience from which a reasoned future path could be chosen. Unfortunately it has been trampled in the rush toward specialization. Not only did it provide a rich background and perspective to the young doctor but the various disciplines benefitted in that they attracted physicians who had made a choice based on genuine understanding and were, therefore, more likely to succeed. The rotating or mixed internship served as an excellent transition for the new physician, offering a broad look at the horizon and a solid foundation upon which to continue. Many considered it the most valuable year of their training.

Almost all students cringe at the prospect of an extra year of training. Yet it seems reasonable that a first, postgraduate year spent rotating through the major medical subdivisions would offer training at least as valuable as that now spent at a low level of responsibility in a narrow field. Acceptance on a national level of a year of rotating or mixed internship as a first year of postgraduate training would offer the medical student a broad and clinically valuable experience from which to choose a career–without exacting a year of penalty.

Certainly the need for additional guidance and expe-

From the Department of Surgery, Mount Sinai School of Medicine of The City University of New York, New York, N.Y.

* Mr. Libin is a fourth-year medical student, Mount Sinai School of Medicine.

Requests for reprints should be sent to Dr. Schwartz, 715 Park Ave., New York, N.Y. 10021.

rience in making a career choice is felt by most students at Mount Sinai School of Medicine. No better vehicle has been devised to satisfy this requisite in a useful time sequence than the rotating or mixed internship. It not only fills the void but is flexible enough to be modified for special purposes or interests. A national effort to restore this faithful servant to a position of respect and service would be a valuable addition to a medical education that meets the needs of our students and our profession.

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CLINICOPATHOLOGIC NOTES

Stephen A. Geller, M. D. and Fiorenzo Paronetto, M. D., Coeditors

Rapidly Progressive Dementia with Focal Neurologic Deficits in a Fifty-seven Year Old Woman*

JAMES T. CAROSCIO, M. D. **WILLIAM O. WHETSELL, JR., M. D., and DAVID C. CODDON, M. D.

Case Report

A 57-year-old right-handed white female was admitted to the neurology service of The Mount Sinai Hospital, with a chief complaint of unsteady gait of four-weeks duration and slurred speech for three weeks.

One month prior to admission, she noted dullness over the right lower extremity. This was followed by difficulty walking which she characterized as unsteadiness and as progressive. She also noted the onset of a generalized headache and a pressure-like pain in the right calf that was constant and nonradiating. She took Darvon, one to two tablets per day, for control of these pains.

Three weeks prior to admission, she noticed the onset of slurred speech and, during the two weeks prior to admission, she experienced nausea and vomiting upon rising in the morning. Her son noted that she was dropping objects. Visual disturbance, change in bowel or bladder habits, and weight change were all denied.

A concussion and fractured jaw resulted from an assault, thirty years previously. Five years prior to admission, the patient had consulted a physician with complaints of nervousness and lightheadedness for which she was prescribed Librium 10 mg and Stelazine 2 mg daily. She smoked one and one-half packs of cigarettes per day.

Her father died of lung carcinoma at the age of 61 and her mother, who had diabetes mellitus, died of a stroke at age 61.

She admitted to shortness of breath when walking one to two blocks and urinary frequency with nocturia times five.

On physical examination, her temperature was 98.6°F, pulse 86 and regular, respirations 20, and blood pressure was 150/90 mm Hg. She was well developed and well nourished. On auscultation of the lungs there were decreased breath sounds. An increased AP diameter of the chest was also noted. The remainder of the general physical examination was normal. During neurologic evaluation, she was described as disheveled and anxious. Although alert and oriented, she could not reverse spell her first name (Rosa) and her calculations were poor. She could not recall the name of the President. Cranial nerve testing revealed dysarthric speech. Motor examination revealed bilateral weakness of hip flexion and slight weakness of left knee flexion and extension. Foot tapping and pivoting were impaired bilaterally, right greater than left. The tone was normal, there was no atrophy. The reflexes were 3+ throughout with sustained clonus at the left ankle. The plantar response was extensor on the left and equivocal on the right. Sensory exam was intact to all modalities. Her gait was broad based. Finger-to-nose and heel-to-shin testing showed bilateral ataxia, right greater than left. Rapid alternating movements were impaired bilaterally and the Rhomberg was positive with the patient falling to the right.

Routine admitting laboratory data were all normal. VDRL was nonreative. There was a trace of protein on urinalysis. T4 was normal at 5.0 $\mu g\%$. Chest x-ray showed over inflation of the upper lobes as seen in bullous disease and there was interstitial fibrosis in both bases. An ECG showed normal sinus rhythm with an intraventricular conduction defect. The opening pressure on spinal tap was recorded at 160 mm H_2O. The fluid was clear and colorless with a protein of 136 mg% and a glucose of 69 mg%. Four red blood cells, and ten white blood cells were noted per mm^3 (2% polys, 86% lymphs, 12% monos and 5% large mononuclear cells). The CSF VDRL was nonreactive.

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* Presented at Neurology Grand Rounds, The Mount Sinai Hospital, October, 1976.

From the Departments of Neurology and **Pathology (Division of Neuropathology), Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Requests for reprints should be sent to James T. Caroscio, M. D., Department of Neurology, The Mount Sinai Hospital, 1 Gustave Levy Place, New York, N.Y. 10029.

By the third hospital day (HD) the patient was described as bradyphrenic, disoriented to time and making aphasic errors. Questionable blurring of the nasal margins of the optic discs was noted on funduscopy. An EEG was read as diffuse cerebral dysfunction with a moderate amount of 4–7 cps activity and a small amount of 1.75–3 cps in frontotemporal derivation. Dexamethasone 4 mg orally, every six hours was started on the fifth HD. A bilateral brachial angiogram was normal except for considerable narrowing of all intracranial vessels, especially in the region of the anterior cerebral artery. A computerized axial tomogram (CAT) done on the ninth HD showed some degree of cerebellar atrophy and prominence of the sulci over the convexities (Fig. 1b). By the 12th HD, cervical and trunchal rigidity was noted and the patient would not move her eyes to verbal command or follow objects, though she insisted she was doing so. A pneumoencephalogram showed marked widening of the sulci on the medial aspect of the hemispheres and over the cerebellum (Fig. 1a). CSF analysis at the time of PEG showed a glucose of 93 mg%, protein of 50 mg% with one rbc and four wbc's per mm^3.

From the 13th through 25th HD, the patient became increasingly confused, required restraining, sustained several falls trying to get out of bed, was described as disoriented to place and time, and was unable to ambulate without assistance. SMA 12 showed elevation of alkaline phosphatase to 108 Bodansky U and gamma GTP to 72 U.

On the 26th HD, a brain biopsy was performed with the specimen taken from the right frontal lobe. The pathology report stated "cerebral cortex and white matter (non-diagnostic)." Confusion increased, she began clinging to nurses, and dystaxia became more pronounced.

On the 46th HD, she had a grand mal seizure and on the following day, two more. Dilantin 400 mg per day was started. Further deterioration was noted. She was described alternately as lethargic and agitated and she became incontinent of urine and feces. On the 60th HD, a technetium brain scan showed decreased flow in the left middle cerebral artery distribution and increased uptake in the region of the brain biopsy. On the 78th HD, she was described as lethargic and tachypneic. Her temperature spiked to 104°F and a chest x-ray showed bilateral infiltrates. Antibiotics were started. On the 83rd HD, she was found without spontaneous respirations, pulse or blood pressure.

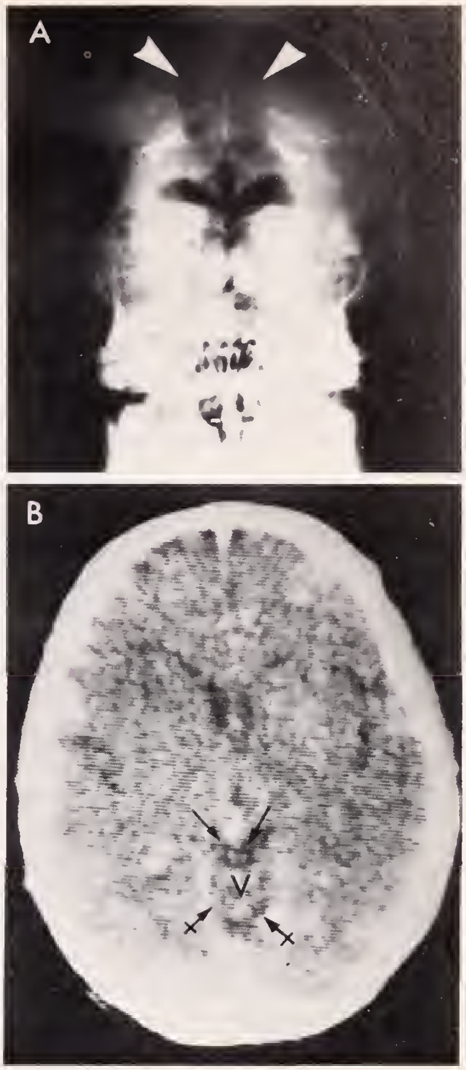

FIG. 1. A. Pneumoencephalogram, anteroposterior view. There is marked widening of the sulci on the medial aspect of the hemispheres along the cingulate sulci (arrow heads). B. Computerized axial tomography of the head with contrast material. There is moderate dilatation of the fourth ventricle (arrows) and superior cerebellar cistern (crossed arrows) with some visualization of the superior vermis (V) consistent with some degree of cerebellar atrophy.

Neurologist's Discussion

In summary, this was a 57-year-old female with a four-week history of unsteadiness on walking and dysarthria. She was found on admission to have an organic mental syndrome, paraparesis, diffuse hyperreflexia with bilateral Babinski signs, and bilateral ataxia. Over a period of four months in the hospital, she showed relentless deterioration with increase in dementia and neurologic deficits; she developed seizures and eventual bilateral pneumonia and died.

There is nothing in the family history, past medical history, general physical examination or initial lab data to give us a lead in this case.

The admitting neurologic findings, with the history of headache, and nausea and vomiting upon rising most likely led the patient's doctors to suspect a posterior fossa mass lesion. Compression of the brain stem and aqueduct by such a lesion would give rise to a noncommunicating hydrocephalus and would have accounted for all of the patient's deficits, except, perhaps the paraparesis. The CSF protein of 136 mg% and the report of blurring of the nasal margins on funduscopic examination added further support to this diagnosis. The normal opening pressure on LP and the presence of a paraparesis were against the diagnosis of a posterior fossa mass. Nevertheless, the patient was started on Dexamethasone, probably with the thought that there was an intracranial mass lesion present.

The CAT scan and PEG, by demonstrating the cortical and cerebellar atrophy, explained all neurologic findings. The cortical atrophy is most marked on the medial aspect of the frontal lobes; hence the paraparesis, increased reflexes, and bilateral Babinski signs. The ataxia is explained by the cerebellar atrophy. The correlation of neurologic deficits with CAT scan and PEG findings is, therefore, complete. But these tests do not give us a diagnosis. We are left with the problem of finding a neurologic condition that results in both cortical and cerebellar atrophy, and runs a clinical course, of relentless deterioration over five months.

A differential diagnosis, should start with the least likely possibilities and progress to the most likely.

Least considered is a toxic etiology because of lack of history of exposure. Carbon monoxide poisoning and hypoxia are known to cause cortical atrophy, but these etiologies are also eliminated by the history. There is no underlying metabolic disturbance so this, too, is ruled out.

A history of trauma thirty years prior to admission is given, and cortical atrophy is well described as a sequela of trauma to the brain. This may partially explain, the patient's PEG and CAT scan findings, but it bears no relationship with the disease responsible for the patient's demise.

Is vascular disease a possibility? An angiogram showed all cerebral vessels were small, especially the anterior cerebral arteries. Since these feed the part of the brain that the PEG so graphically demonstrated to be atrophied, interesting possibilities are conjured up. However, there is no localized narrowing of vessels or tortuosity which would suggest widespread arteriosclerotic cerebrovascular disease.

Is an infectious etiology feasible? General paresis can cause cortical atrophy, especially in the anterior portions of the frontal and temporal lobes, but the course of general paresis is prolonged and the patient had a negative CSF VDRL which virtually excludes lues as a diagnosis. Clinically, there was no fever, lethargy, stupor or coma that would have suggested encephalitis. SSPE is now believed to be an infectious disease, but the oldest patient reported in the literature was twenty-eight; since this is a disease that runs a longer course, it does not merit serious consideration.

Is a primary or metastatic CNS neoplasm possible? Robertson, stresses the point that atrophy and neoplasm may coexist, and recognition of a neoplasm in an atrophic brain on PEG may be impossible (1). An angiogram and a CAT scan, however, failed to indicate the presence of a mass lesion in the patient, which rules out an intracerebral neoplasm.

How about the cerebellar degenerative diseases like spinocerebellar degeneration or olivoponto cerebellar degeneration? Twenty percent of these patients have mild mental changes (2), but dementia is not a major part of the clinical picture, and these diseases run a much more insidious course. Arieff and Kaplan described five cases of a nonfamilial, nonhereditary disease they called cerebrocerebellar atrophy (3). Their patients had dysarthria, cerebellar ataxia, intention tremor, involvement of the pyramidal tracts, and at times dementia and convulsions. The course was prolonged and not particularly morbid (no patient died) and dementia was only a minor feature. In those patients in whom dementia was present, there was a history of ethanol abuse. (No history of ethanol abuse was given with our case.)

Cerebellar atrophy is well described in alcoholism but the ataxia with this type of cerebellar degeneration is typically confined to the trunk and lower extremities and the course is insidious (our patient had ataxia of all four limbs).

Is it clinically feasible that this patient had multiple sclerosis (MS)? Twenty to thirty percent of patients with MS have an onset of symptoms after age 40; thirty percent run a progressive course (4), and acute MS with death reported within a few weeks is well documented.

Is cortical or cerebellar atrophy a feature of MS? Boudin and Barbizet in 1954 reported on 33 patients with MS whose PEG's showed cortical atrophy (5). This was mostly frontal in the eight patients in whom dementia and euphoria were major signs of their disease. In 1976, Gyldensted reported on CAT scans done on 110 MS patients. Forty-five percent of the patients had evidence of cerebral atrophy. However, the average duration of disease in these cases was 19 years (6).

In Schilder's disease, adult cases are reported, a subacute form is described, and in adults the disorder begins with signs of local brain disease. Also, mental signs can occur early, cerebellar signs may develop, and limb paralysis with increased reflexes and positive Babinski signs are well described. Progressive loss of vision is frequent and seizures are rare, however.

There are also adult forms of metachromatic leukodystrophy, but this is a systemic disease with a more insidious course, and visual signs are generally a major feature.

Progressive multifocal leukoencephalopathy is yet another demyelinating disease, but this occurs almost exclusively in the presence of lymphoproliferative or myeloproliferative disease (though it has been reported in patients with TB, sarcoid, and carcinoma). It was not seriously considered here. Clinically, any one of the demyelinating diseases could be a possibility, if not a probability, and should not be categorically ruled out, but they are not of serious consideration because of the diagnostic information obtained from the PEG and CAT scans. These studies showed marked atrophy over the convexities while the ventricular size remained virtually normal. This suggests a disease of the cortex or grey matter, as opposed to the subcortex or white matter.

So what about the cortical diseases? Alzheimer's and Pick's disease can be eliminated from consideration surprisingly quickly. True, cortical atrophy is a prominent feature, as is dementia, and seizures do occur as does aphasia; and all of these features fit the case at hand. However, focal neurologic deficits are not a feature of either of these diseases except very late in the course. The course is also much more prolonged and the cerebellum is virtually never involved. Dow and Moruzzi found reports of the combination of Pick's disease and cerebellar atrophy recorded a few times, but no clear basis for their association was evident, and the conclusion was that they were dealing with two diseases. (We may be also, but it is assumed otherwise). They were able to find only one reported case of Alzheimer's disease with cerebellar atrophy, and in this patient, there were no cerebellar deficits on neurologic examination. The atrophy was felt to have been related to birth trauma (7).

What is left, then, as etiologic possibilities? What disease states can cause dementia, focal neurologic deficits, cortical and cerebellar atrophy, and are progressive enough to end in death after a 5-month course? There are two such diseases and a good case can be made in favor of either one. They are Jakob-Creutzfeldt disease, and diffuse polioencephalopathy, a remote effect of cancer on the nervous system.

Jakob-Creutzfeldt disease is a rapidly progressive disease with chief clinical features of dementia, upper and sometimes lower motor neuron disorders, basal ganglia and cerebellar dysfunction, seizures, and myoclonus with a heightened startle reaction. Pathologically, the changes of neuronal loss, astrocytosis and status spongiosis are present in the neocortex, striatum, thalamus, cerebellum and motor pathways. The neuronal loss is most severe in the cerebellum. It is, of course, a transmissible disease with a slow virus etiology. Kirschbaum in his monograph on Jakob-Creutzfeldt disease (8) reviewed 150 cases in the literature. Sixty-three of 150 had some degree of cortical atrophy and cerebellar atrophy is specifically described in one case. Usually only mild to moderate convolutional atrophy is present, but pronounced atrophy, as our patient had, has been described. In Kirschbaum's review, 108 of 150 patients had disturbances of speech and 39 had symptoms of cerebellar ataxia. Forty-six percent died within six months of onset of symptoms, and 38% were between the ages of 51–60.

Kirschbaum divided the clinical manifestations into three stages:

1) Vague complaints of physical discomfort, odd and painful sensations, apprehension, forgetfullness and slight gait and speech disturbances.
2) More severe mental aberrations occur with aphasia, cortical, pyramidal and extrapyramidal dysfunctions. Seizures, rare in the beginning, increase in frequency. Myoclonic phenomenon occur and amyotrophy resembling ALS can occur. (There is much overlap between the first and second stages).
3) A vegetative existence characterized by mutism, akinesia, myoclonic and epileptic seizures, decerebrate rigidity and semicoma. Cerebrospinal fluid studies show a lymphocytosis of up to 15 cells and the CSF protein can range from 50–120 mg%. The EEG often shows a continuous pattern of diffuse or more focal theta and delta activity of rather high amplitude on a background of depressed alpha frequency. Later periodic synchronous high voltage wave and spike discharges at one to several seconds occur, which may or may not be accompanied by myoclonic jerks.

Our patient did not have myoclonus or a startle response, nor did her EEG show the high voltage periodic spike and wave activity. How unlikely does this make Jakob-Creutzfeldt disease as a diagnosis?

The so-called typical EEG changes are only present in one half of the cases and Merritt states that myoclonus occurs in only 46% of cases (9). Furthermore, our patient expired with pneumonia somewhere in the second stage before EEG findings or myoclonus are common.

Finally, the last considered diagnosis for this case is an entity which is not clearly defined–diffuse polioencephalopathy, a remote effect of carcinoma.

Where is the carcinoma in our patient? She was a one and one-half pack per day smoker, offered symptoms of shortness of breath, and her admitting chest x-ray and physical exam were consistent with emphysema and

COPD. No mention of a lung lesion is made on the official admitting x-ray report, but on reviewing that film, the radiologists retrospectively see a possible coin lesion in the left lower lobe. It does not appear on later films, though they are of poor quality.

It is not unusual for neurologic abnormalities to precede discovery of the associated neoplasm by as many as 36 months (10). (Our patient died after only five months). Brain and Wilkenson noted that ten out of 17 patients they reviewed had neurologic symptoms that preceded discovery of their tumors (11).

Dow and Moruzzi discuss an entity known as subacute cerebellar degeneration (7). The patients frequently complained of pains in the legs as early symptoms, CSF at times showed a lymphocytic pleocytosis, and an increased CSF protein was frequent. Most remarkably, there was an associated carcinoma in 11 of 16 cases (three had cancer (Ca) of the lung, five, of the ovary).

Croft and Wilkenson listed cerebellar degeneration as third in frequency to carcinomatous neuropathy and myopathy among the carcinomatous encephalopathies and stated it occurred in 9% of patients with malignant disease (more specifically, in 11% of patients with carcinoma of the breast or lung and 27% of patients with carcinoma of the ovary) (12). Morton, in 1966, stated that 37% of patients with bronchogenic Ca have it (13).

Typical clinical features of this type of cerebellar atrophy is ataxia of the trunk, lower and upper extremities. Dysarthria is prominent while nystagmus is not. Croft and Wilkenson also noted that dementia was sometimes prominent.

In 1964, Brain and Norris' classic symposium on remote effects of cancer on the nervous system (14) appeared, and they recognized three forms of encephalopathy in their classification of nonmetastatic carcinomatous diseases. Multifocal leukoencephalopathy was first and we have already dismissed it from consideration; second, encephalopathy caused by disordered metabolic, endocrine or nutritional deficiency, (not applicable in this case); and finally, diffuse polioencephalopathy, pathologically characterized by widespread loss of ganglion cells in grey matter. They further subdivided this encephalopathy into:

1) Those with mental symptoms which consisted of a wide range of psychiatric disorders, a simple dementia that was fairly rapid and progressive, or a disorder of memory, with or without, confusion and disorientation. These symptoms were sometimes associated with focal cerebral signs and vice versa.
2) Subacute cerebellar degeneration which we have already mentioned; but this clinical entity was further elucidated by Brain and Wilkenson in this same symposium (14) when they reviewed a series of 17 patients. In 14 of 17 dysarthria was present, 11 of 17 had difficulty swallowing, four had weakness of limbs, three complained of pain as an early symptom, three complained of numbness but there was no sensory deficit. Two of 17 had increased deep tendon reflexes, six had bilateral Babinski signs, and nine were demented. Two of 17 had a CSF pleocytosis of from 11 to 20 cells, four had elevated CSF protein, seizures were a common feature, and finally, death within three to four months occurred in several cases.
3) Brain stem lesions which may occur in association with the first two subdivisions. When the upper brain stem is mainly involved, the symptoms are those of ophthalmoplegia or gaze paralysis (recall the patient's inability to move her eyes on command or to follow objects). When the lower brain stem is chiefly affected, there may be severe bulbar palsy, (difficulty swallowing was noted late in the patient's course).

Yahr, Duvoisin and Cowen, in 1965, stated "on reviewing cases of carcinomatous neuropathy, one notes a significant incidence of mental disturbance. Mental disturbance may not only comprise a very prominent part of the clinical picture, but they may in some cases be the initial neurologic manifestations or sole manifestation (15)." They discussed a patient, later found to have carcinoma of the lung, who had a marked memory loss; and at autopsy, was found to have lesions in the grey matter of the temporal lobes.

Corsellis, in 1968, called this limbic encephalitis (16). This is yet another form of carcinomatous encephalopathy.

The outstanding feature of our case, as demonstrated by the diagnostic studies, was the cortical and cerebellar atrophy. This, too, has been described as a feature of diffuse polioencephalopathy upon inspection of the brain at autopsy (17).

In summary, clinically, both Jakob-Creutzfeldt disease and remote effects of carcinoma seem to describe our patient. Choosing between the two for a diagnosis is difficult. Because there was a possible coin lesion on the admitting chest x-ray in this case, remote effects of carcinoma was chosen as a final diagnosis here. It is predicted that at autopsy, the patient was found to have carcinoma of the lung. The elevated alkaline phosphatase and gamma GTP were secondary to liver metastases of that carcinoma and on microscopy her brain was noted to have a diffuse loss of ganglion cells which is typical of diffuse polioencephalopathy.

Pathologist's Discussion

Operative Findings

The specimen consisted of four small pieces of gray-white cerebral cortical tissue, the largest of which measured 0.9 × 0.3 × 0.2 cm. The entire specimen was embedded and examined by light microscopy. The sections demonstrated normal-appearing cerebral cortex and subcortical white matter. There was no evidence of inflammatory or degenerative change.

Surgical Diagnosis

Cerebral cortex and white matter (nondiagnostic).

Autopsy Findings

When this case came to autopsy, the working diagnosis was Creutzfeldt-Jakob disease. (Editor's Note: Though most descriptions of this condition refer to it as Jakob-Creutzfeldt Disease, historically the first description of a case was by Creutzfeldt in 1920. In 1921, Jakob wrote a more detailed paper in which he cited Creutzfeldt's original report. For this reason of chronology, there has been a recent tendency in some quarters to refer to the condition as Creutzfeldt-Jakob Disease, as the pathologist does here.) Since this has been shown to be a transmissable disease, the usual precautions for handling the brain were taken (18).

The fresh brain weighed 1,260 grams. Gross examination of external surfaces showed a mild focal cortical atrophy bilaterally and symmetrically over the convexities at the frontoparietal junctions. There was no evidence of atrophy anywhere else in the cerebral hemispheres, brainstem, or cerebellum. The bilaterally symmetrical focal cerebral atrophy in the fresh brain was significant enough to be obvious. It was compatible with the picture given by the pneumoencephalogram (Fig. 1). However, it seemed curious that the atrophy was not more widespread. It was also striking that there was not evidence of cerebellar atrophy as had been demonstrated on PEG and CAT scan. Because of the results of the two studies, we particularly noted the cerebellar configuration in the fresh brain. There was no evidence of decreased size of the cerebellum or its peduncles and the folial configuration showed no atrophic changes, such as, abnormal widening of sulci.

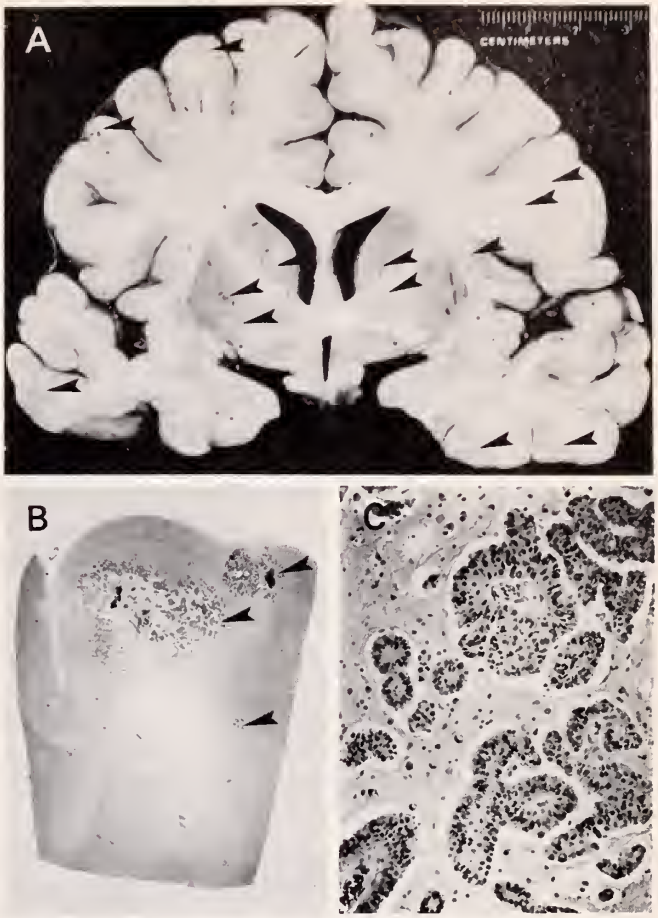

FIG. 2. A. Coronal section of the cerebral hemispheres at the level of the frontoparietal junction. Arrows indicate locations of the multiple nodules of neoplasm widely distributed throughout the section. Note minimal widening of the cingulate sulci and the superior frontal sulcus on the right side of the section. B. Low-magnification photograph of a histologic section of left middle frontal gyrus. Note there are three separate nodules of neoplasm (arrows) located in cortex, at corticomedullary junction, and in white matter (Mag. ×10). C. Microscopic appearance of a neoplastic nodule in the cerebral hemisphere. Tumor cells are arranged in a glandular pattern distinct and well-circumscribed in the brain parenchyma (Mag. ×140).

The brain was fixed for two weeks in neutral formalin (10%) before any dissection was carried out. Following that fixation, the brain was reexamined grossly over all its external surfaces. The focal, bilaterally symmetrical cerebral atrophy remained obvious at the frontoparietal junction over the convexity of either hemisphere. Otherwise no abnormalities were noted. The cerebral hemispheres were cut into 1 cm coronal sections and the brainstem and cerebellum were cut into 0.5 cm horizontal sections. During the cutting and examination of all the cut surfaces, the striking observation was that there were many small white, somewhat caseous-looking nodules throughout gray and white matter of both cerebral hemispheres (Fig. 2), the brainstem, and the cerebellum. The largest of these nodules measured about 1 cm in diameter; the smallest grossly visible nodule was about 0.2 cm in diameter. There appeared to be no particular distribution of the nodules,–no predilection for white matter, gray matter, cortico-medullary junction, superficial structures or deep structures. There was no leptomeningeal involvement. In two of the coronal cerebral sections, we counted as many as 18 distinctly independent nodules. In the brainstem and cerebellum, there were several nodules of the larger size (approximately 1 cm in diameter) in midbrain tegmentum, basis pontis, right middle cerebellar peduncle, deep cerebellar white matter, and upper medulla. Sections of the spinal cord showed no evidence of the nodular involvement.

The presence of these multiple small nodules, raised the possibility of a granulomatous infection with miliary dissemination in the central nervous system. One might expect an involvement of the leptomeninges, also, if there were a generalized dissemination of the infection to the central nervous system. There was no gross evidence for such involvement. Another immediate consideration was the possibility of a neoplasm. A primary neoplasm of brain is rarely multicentric or multifocal, and does not give the gross appearance of these multiple small nodules. A metastatic neoplasm must certainly be included. The fact that there were so many nodules in such a diffuse distribution and all of such relatively small size would mitigate against a metastatic lesion, however. There was also no evidence of a primary neoplasm demonstrated during the clinical course.

Thus far, there was no definitive evidence for a diffuse degenerative process, therefore no gross evidence of slow-virus disease. It is important to note here, however, that except in later stages of spongiform encephalopathy, examination of external or cut surfaces of brain may reveal no grossly visible changes (8). It is only after there is rather severe cortical degeneration that the typical cortical atrophy may be grossly visible (8).

The multiple small white nodules received our immediate attention for two reasons. First, they appeared to be decidedly unusual for any pathologic process, infectious or otherwise, in the central nervous system, because of their remarkable number and their broad distribution throughout the cerebrum, brainstem, and cerebellum, but not the spinal cord. Second, the possibility of a widely disseminated, caseating infection, though remote, would not be impossible and should be ruled out quickly. With those two thoughts in mind, several sections were taken from the fixed gross brain and processed rapidly for hematoxylin and eosin stain.

On the day following the gross examination, sections from seven different nodules, each from a different region of cerebrum, brainstem, or cerebellum, were examined microscopically. In every sample, the examination revealed a poorly differentiated but well-circumscribed adenocarcinoma. Samples of other nodules, submitted in routine fashion and returned for microscopic examination with the rest of the nervous system specimens, were all of identical appearance.

There was no evidence of infection, inflammation, caseation, or granulomatous reaction. Furthermore, in multiple samples of cerebral cortex (all lobes, bilaterally), basal ganglia, thalamus, and cerebellum, there was no evidence of cortical atrophy or spongiform change. Paying particular attention to the focal, bilateral cortical atrophy observed on pneumoencephalogram and grossly at autopsy, there was no microscopic evidence of cortical cell loss, glial proliferation or loss of normal cortical architectural configuration. The gross observation of focal atrophy coupled with the normal microscopic appearance indicates that the bilateral but focal and symmetrical atrophic configuration of the cerebral hemispheres might have resulted from an unusual anatomical variation in cortical configuration and not cortical atrophy.

Returning to the general autopsy, an incidental and unexpected finding was the presence of a number of small, discrete, whitish nodules in lungs, paratracheal lymph nodes, adrenals and kidneys, bilaterally. The largest of these nodules measured only 0.5 cm. The nodules, examined microscopically, showed foci of poorly differentiated neoplastic cells arranged in glandular pattern, with signet ring shape, significant pleomorphism and hyperchromatic nuclei. This appearance was the same in all the organs involved. Though the neoplasm was so poorly differentiated that it was not possible to positively identify its primary origin, the distinguishing histologic features coupled with the patterns of metastasis strongly suggested its origin from the lung.

The neuropathologic findings in this case kept everyone in suspense for some time after the autopsy was performed. Appropriately, with the high index of suspicion for slow-virus disease we were careful to use an established protocol of procedure for handling such cases. As it turned out, there was no apparent relationship of the clinical symptoms to any sort of infectious process, slow virus or otherwise, but the age of the patient, the clinical course, and even several important laboratory findings were compatible with the diagnosis of Creutzfeldt-Jakob disease (8).

It is rare to find such widespread distribution of a metastatic malignancy in the nervous system, and usually when widespread lesions are present, at least some of them are demonstrable by clinical tests, such as, arteriography or computerized axial tomography. In this case, even though there were at least 35 to 40 distinctly independent metastatic lesions throughout cerebrum, brainstem, and cerebellum, no single lesion was larger than 1.0 cm in diameter and no single lesion could be demonstrated by arteriography or scanning procedures, even retrospectively. It is compatible with the limits of resolution of these techniques that such small unsuspected lesions could not be demonstrated.

The consideration of remote effect of carcinoma on the central nervous system cannot be ruled out. Although there were widespread, focal lesions throughout the cerebrum, brainstem, and cerebellum, some of the more diffuse or less focal symptoms in this patient might not be clearly attributed to these small focal lesions. As previously mentioned, some of the more nonlocalizing symptoms observed in this individual may, indeed, have been secondary to remote effects of carcinoma (15).

In conclusion, this case represents an unusual presentation and manifestation, both clinically and pathologically, of a rather common pathologic entity. If we consider that the site of origin of the neoplasm was the lung, then we are seeing a neoplasm that, certainly by most statistical analyses, is among the two or three most frequent metastatic lesions in the brain (19). Not only does such an unusual presentation of such a common disease generate special interest from the point of view of the pathologist, but it also bears consideration in the clinical differential diagnosis of the degenerative neurologic diseases and dementias.

COMMENT

Attending Physician

When I first saw this patient for consultation in my office, the history and findings made me strongly suspicious of a lesion involving the posterior fossa and a neoplastic process, very likely metastatic in nature, was favored. In fact, her admitting diagnosis was so labeled. All of the etiologic possibilities discussed by Dr. Caroscio were considered. As each diagnostic study failed to demonstrate a specific etiology, most of our thinking was funnelled towards a diagnosis of Jakob-Creutzfeldt disease. This was certainly reasonable when one considered the total picture. One other antimortem diagnosis I had considered was disseminated tuberculosis. It is noteworthy that her rather common neurologic disease entity completely eluded a most comprehensive and orderly workup and finally was only revealed by microscopic examination of postmortem tissue.

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Student's Corner

PAUL CELANO, B.S., Editor

Prospects for Clinical Epidemiology in Prepaid Group Practice

LESLIE ALHADEFF, B.A.

Abstract

This paper presents three organizational factors that could make the prepaid group practice, health-care delivery setting particularly suitable for implementing clinical research. Examples of clinical research using these factors are presented and discussed. Methodology involved participant observation, and personal interviews with members of a large, prepaid group practice on the west coast in addition to a literature review. Present limitations and future prospects for clinical epidemiology in this setting are also included.

Introduction

Prepaid group practice (PPGP) health plans are organizational settings where relatively little medical research has been done. The characteristics of these organizations, their growing number in the United States, and their potential for large data bases provide new and valuable alternatives to the researcher.

Of the three types of medical research (basic, clinical, and health services research), the most frequently observed up to now in PPGP settings has been health services research (1, 2). For example, it has been highlighted that the major research activity at Kaiser Permanente, the largest plan of the sort in the country, is health services research (3). It has been identified that "the complete accessibility of all clinic material through the unit record system and the accessibility of the whole range of comprehensive benefits in one system together with the known population base are what makes this the ideal milieu for research in the delivery of health services (4)."

Recently, some researchers have begun to recognize the great advantages PPGPs may offer as systems in which projects in clinical epidemiology would be conducted. MacMahon and Pugh stress that the use of PPGPs may be "advantageous in cohort studies since they offer mechanisms for periodic follow up and their records are complete and readily available (5)." Jick, describing the methodology needed to research drug illness, finds that comprehensive health plans are useful in relation to drug illness because they offer a "complete and accurate long-term record of drugs taken by a large, defined population (6)." Hurst puts it this way: "The well defined health plan population is demographically and socio-economically representative of the community and therefore offers a ready made study group (7)."

The author of this paper, as a medical student, was given the opportunity to observe and analyze the organization of a PPGP on the west coast. The purpose of this paper is to identify and describe the basic organizational factors which make the PPGP setting particularly suitable for the implementation of clinical research projects. To highlight these factors, examples of the types of clinical research projects conducted at the observed PPGP and other PPGPs in the country are discussed.

Materials and Methods

This study was performed at Group Health Cooperative of Puget Sound (GHC), a consumer governed, prepaid group practice plan that serves an enrolled population of over 250,000 who live in Seattle, Washington (8,

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This paper was written during Mr. Alhadeff's third-year community medicine clerkship.

Requests for reprints should be sent to Mr. Leslie Alhadeff, 12 East 86th St., New York, N.Y. 10028.

9). The author conducted this study as a research assistant at GHC and to fulfill the requirements of the community medicine clerkship at Mount Sinai School of Medicine.

Three basic methodologies were employed. First a review of the literature was conducted with particular focus on papers that a) addressed organizational factors in various prepaid group practice systems in the United States, and b) reported research experiences in these same systems.

Second, participant observation was used as a means of understanding the structure, organizational variables, and functions of one system as well as to gain insight into the research potential of this type of system in general.

Finally, open interviews were also carried out with physicians, consumers, and administrators to obtain further insight into the organization and prospects for clinical epidemiology in this system.

Discussion

Three organizational factors that were identified, though present in the prepaid group practice system primarily to fulfill a service goal, seem to be particularly significant features that make the conducting of clinical research there particularly attractive:

a) the system serves a defined population.

b) the members enrolled in the system are entitled to a comprehensive medical care coverage.

c) the system owns and controls all of the facilities needed for the provision of services, allowing centralization of medical records and computerized access to these records.

Defined Population

The PPGP identifies through prepayment and capitation all persons who receive health care for which it is responsible, that is its membership (4). This allows the PPGP to identify the characteristics of the enrolled population prior to the appearance of a disease under investigation. Such a defined population provides a denominator for clinical epidemiology (5). The importance of relying on appropriate denominator information can be illustrated best with an example that describes a case control study done at GHC regarding their lower rate of surgery for appendicitis:

> Watkins studied appendectomy rates and the rates of perforating appendicitis among different surgeons at GHC (10). He noted that in the treatment of appendicitis, the more aggressive surgeon at GHC, performing 160/100,000 (population) appendectomies per year had the same perforation rate as the least aggressive surgeon performing only 80/100,00 (population) appendectomies per year. Their exposure to cases of appendicitis was roughly comparable.
>
> The perforation rate, using the population denominator available only with a defined population, was 22/100,000 (population) for both surgeons. However, the more traditional case rate analysis that does not use the population denominator erroneously shows the aggressive surgeon had a 14% (22/160) perforation rate, whereas the conservative surgeon had a 28% (22/80) perforation rate.

Therefore in the PPGP, the cases identified can be related directly to the reference (enrolled) population yielding a natural denominator. In the fee for service setting on the other hand, this is not possible. Here the institution only defines members utilizing services at any one moment and cannot define the characteristics of the population for which it is responsible.

Comprehensive Medical Coverage

Because comprehensive medical coverage is offered by the PPGP, the population served may receive all of its medical care from that system, even in emergency situations (11). This assures the researcher of important research parameters. First, it assures that members' records will reflect the total care each individual has received helping the researcher accurately describe a cohort retrospectively. For example, out-system use of health services at GHC is estimated to be less than 10% (12). This is unlike the fee-for-service setting where the population will use multiple facilities and their records at any one institution may reflect only part of the total care they have received. Moreover, the comprehensive coverage offered assures the researchers that most members will continue exclusively using the system as a study progresses, therefore greatly facilitating follow-up of a cohort prospectively.

This feature greatly increases the researcher's ability to fully describe both the numerator and the denominator in retrospective or prospective studies and is, therefore, important in dealing with the dropout, either due to resignation of members from the PPGP or refusal of some members to participate in studies. In the former case, the completeness of the records helps in comparing the characteristics of those resigning their membership to the characteristics of the rest of the membership. In the latter case, the characteristics of a group agreeing and a group not agreeing to participate in a study can be described and more importantly can continue to be monitored since both groups remain members. In both cases the ability to fully describe the characteristics of these groups is important; otherwise, bias might be introduced if a selective dropout were to occur. The above can best be illustrated using the following example describing an interventional cohort study conducted at HIP (Health Insurance Plan of New York) regarding breast cancer screening:

> In 1963, HIP began a long-term interventional cohort study (13–16) on whether "periodic breast cancer screening with

mammography and clinical examination results in a reduction in mortality from breast cancer in the female population (16)." Because HIP had an enrolled population with complete records the "comparison could be made between the experience of the total group of 31,000 women offered screening whether or not they accepted (only 60% accepted) with that of a comparable control group not offered screening . . . (16)" This was important since the women who accepted screening differed from women who did not. "The relatively low rate (incidence rate of histologically confirmed breast cancers) in the group not accepting screening examinations suggests that study women with a higher risk for breast cancer tended to self-select themselves for screening (16)." There was no reasonable way of offering the control group participation in the study without having them know they were in the control group (eliminating assignment blinding). If just the study group had been compared to the control group, breast cancer mortality might have been erroneously lower for the study group. HIP, however, was able to describe the rate of breast cancer in those women who did not accept screening as well as in those who did and therefore was able to compare the entire group offered screening to the entire group not offered screening, avoiding serious problems.

Ownership, Centralization and Computerization

The PPGP system owns and controls all the facilities needed for the provision of services. Patients receive their care from the same hospital, group of doctors and labs. Therefore, the services rendered and the records kept are uniform.

Furthermore, in order to help fulfill its service goals, the system has centralized and brought computer access to its records. The centralization and computerized access to these records also help the researcher to obtain a large number of cases and appropriate controls quickly, thus accelerating the research effort and drastically reducing costs.

This contrasts with research on populations insured on an indemnity basis. Records from their subscribers will be far from uniform if in fact all the necessary records can be retrieved from the various institutions reimbursed by the insurance company. In essence the PPGP combines the accessibility and uniformity of records found within a single institution with the advantages of a defined population in providing appropriate denominator information.

Because of the presence of these organizational characteristics, it was observed that retrospective cohort studies become possible. Usually the only type of retrospective studies done are case control studies, so much so that the word retrospective has been used interchangeably with case control. Conversely, the word prospective has been used interchangeably with the word cohort because most cohort studies have only been conducted prospectively. MacMahon and Pugh have pointed out that the cost of such prospective cohort studies could be substantially reduced if the cause and effect under investigation were such that they could both be ascertained retrospectively from existing records (5). In the PPGP, cause and effect can be ascertained retrospectively because, in most cases, the characteristics of the enrolled population can be defined retrospectively thanks to the completeness of the records (comprehensive coverage), and their uniformity (ownership of facilities). Furthermore, with centralization and computerized access to these records, the research effort is accelerated and costs reduced. The importance of these organizational factors to conducting a retrospective cohort study is best illustrated by the following example that describes a retrospective cohort study done at GHC regarding estrogens and breast cancer:

> Since 1975, GHC has kept a computer record of all drugs prescribed to its members. It also has on computer the discharge diagnoses of all members who have been hospitalized. Jick, in his paper on endometrial carcinoma and estrogen usage, used this computerized data to identify a cohort of women retrospectively from 1975 to 1977 (17). He first identified part of the cohort for whom at least one prescription for a replacement estrogen preparation was filled in that time period. (Since 98% of the membership prescribed to by GHC filled their prescription at GHC, there is little chance that computerized records of estrogen usage would be incomplete (17)). The list of these women was then compared by computer to the data for discharge diagnoses; in this case, women diagnosed for the first time as having endometrial cancer. (The denominator was adjusted for the actual size of the group at risk to include only women with uteri). Put simply, the relative risk for women using estrogens would be greater than one if the number of discharge diagnoses of endometrial carcinoma for them was greater than for the women in the cohort who had not used estrogens.

This type of retrospective study provides the researcher with appropriate denominator information while consuming a fraction of the cost and time normally needed to conduct a prospective cohort study.

Conclusions

Many papers have been written on the advantages PPGPs offer to our health care system (4, 8, 18–23). In this paper, the advantagés the PPGP may offer to clinical epidemiology have been briefly outlined. It was mentioned that PPGPs offer researchers a defined population and, therefore, provide appropriate denominator information. This does not mean that the defined population of the PPGP is necessarily representative of a more general population. The location of the PPGP's enrolled-population and what factors determine its membership must always be carefully studied in order to determine whether study results for PPGP's enrolled population can be applied to other populations. (In the case of GHC, the demographic characteristics of the enrolled population do not significantly differ from those of the United States population in general (12)).

Defined populations can also be found in other settings. Certain obstetric populations, occupational and insured groups also have well-defined populations (5). The advantages the PPGP seem to offer to clinical epidemiology derive not only from the defined population but also from the uniqueness of this defined population. The PPGP's defined population is unique because it offers records that reflect members' total care, are uniform, and are readily available with good mechanisms for follow-up already present. Only in the PPGP can all of these organizational factors be found together. It is this combination of factors that facilitates researchers' efforts, reduces costs and makes certain types of research projects possible.

However, even though these factors are a tremendous resource to clinical epidemiology, one must be reminded that they are present primarily to fulfill service goals that can limit research in this setting. Prepaid group practice is a form of private practice that relies on consumer satisfaction for its existence, growth and development. Research considered in this setting must be appropriate in terms of consumer acceptance and of the fiscal impact it will have on the system. The research done in the PPGP must directly benefit the group as well as respect the rights of patients and physicians (24, 25).

Furthermore, because the doctor-patient relationship in this setting is very personal, it is as difficult to intrude upon as it would be in any other form of private practice. It is clear from the above that some research projects suitable to the system from an epidemiologic point of view might not be able to be carried out because they were thought not to be suitable from a services point of view. The attitude of the researchers and their diligence in involving all those concerned also has a great impact on which research projects will be permitted. More projects may be accepted as research departments, consisting of members who understand the dynamics of the system, become established in many of the PPGPs (7, 18).

PPGPs are a type of health delivery system that is growing rapidly in popularity. Between 1977 and 1978 thirty new PPGPs were started (9). As this type of health delivery system becomes more ubiquitous, expeditious and inexpensive research on a defined population becomes more generally available. Nevertheless, PPGPs have only recently become popular and therefore are relatively small, not having had a chance to develop. In fact, many of the 195 PPGPs in existence in 1978 were only founded in the early 1970's. Only twelve of these PPGPs had enrollments exceeding 100,000 members and one third had fewer than 5,000 members (9). Because of this, few PPGPs have as yet attained enrollments large enough to afford their own hospitals or afford researchers the advantages of a large enough defined population. As this form of health care delivery system gains acceptance however, and the more recently founded PPGPs continue to expand, more PPGPs will come to have large defined populations and own their hospital facilities.

In conclusion, it must be reiterated that the internal goal of this health system is the delivery of services. However, because this system is primarily concerned with services it assumes responsibility for the long-term, comprehensive medical care of a defined population and, therefore, offers very bright prospects for clinical epidemiology.

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Letter to the Editor

Indirect Immunofluorescence Test Against Lymphocytic Choriomeningitis (LCM) Virus in Parkinson's Disease

Dear sir:

The role of viruses in the etiology of Parkinson's disease has been reviewed in several recent communications (1–5). Nucleic acid homology studies of herpes simplex virus type 1 DNA and influenza A/NWS RNA in brain tissues (3), as well as electron microscopy and indirect immunofluorescence studies of virus-coded protein products in the same tissues (4), have yielded no evidence of viral presence. Likewise, viral antibody titers in serum and CSF to 17 arboviruses (2), to 12 strains of influenza A viruses (including swine strains), and to 11 other viruses (HSV types 1 and 2, CMV, V-Z, measles, rubella, mumps, Coxsackie B3 and B4, parainfluenza 1 and influenza B viruses) (5), have failed to show a biologically meaningful relationship between any of these viruses and Parkinson's disease.

Lymphocytic choriomeningitis (LCM) virus, an arenavirus, is transmissible to man from naturally infected house mice and hamsters (6), causing a clinical picture at times similar to that caused by other neurotropic viruses, such as aseptic meningitis or meningoencephalitis (7). Often, the infection is clinically inapparent or produces an influenza-like syndrome. After infection of man, antibodies are detectable early by the immunofluorescence test; it has not been determined how long antibodies persist by this technique, although it is known that they remain positive for several years by the neutralization test (6). In the mouse model, every aspect of the disease, in both the acute and chronic phases of LCM virus infection, is immunologically mediated. That such a model of humoral and cell-mediated immunologic response may ultimately cause a disease following some prolonged viral infections in man, has been considered as a possible process in the development of the so-called "slow virus infections."

Serum specimens were obtained from 29 patients with classical postencephalitic Parkinson's disease, from 45 randomly selected patients with idiopathic Parkinson's disease, and from 50 controls with neurologic diseases other than Parkinsonism and matched for race, ethnic origin, sex and age (± 5 yrs.). Indirect immunofluorescence (6) against LCM virus was tested with sera at 1:4 dilution. (Table I). All sera were negative, except for two—one from a 58-year-old woman with cirrhosis and organic mental syndrome (control), and one from a 65-year-old woman with idiopathic Parkinson's disease.

TABLE I
Indirect Immunofluorescence Test against LCM Virus in Parkinsonian Patients and Controls

Patients	Sera	
	No. Tested	No. Positive
Controls	50	1
Idiopathic Parkinson's Disease	45	1
Postencephalitic Parkinson's Disease	29	0
Total	124	2

To our knowledge, this is the first report on LCM viral antibodies in idiopathic and postencephalitic Parkinson's. The negative result adds yet another virus to the growing list of viral agents that have failed to show a relationship to Parkinson's Disease.

Sincerely,

Teresita S. Elizan, M.D.
Melvin D. Yahr, M.D.
Department of Neurology,
Mount Sinai School of Medicine
of The City University of New York

Jordi Casals, M.D.
Department of Epidemiology
and Public Health
Yale University School of Medicine

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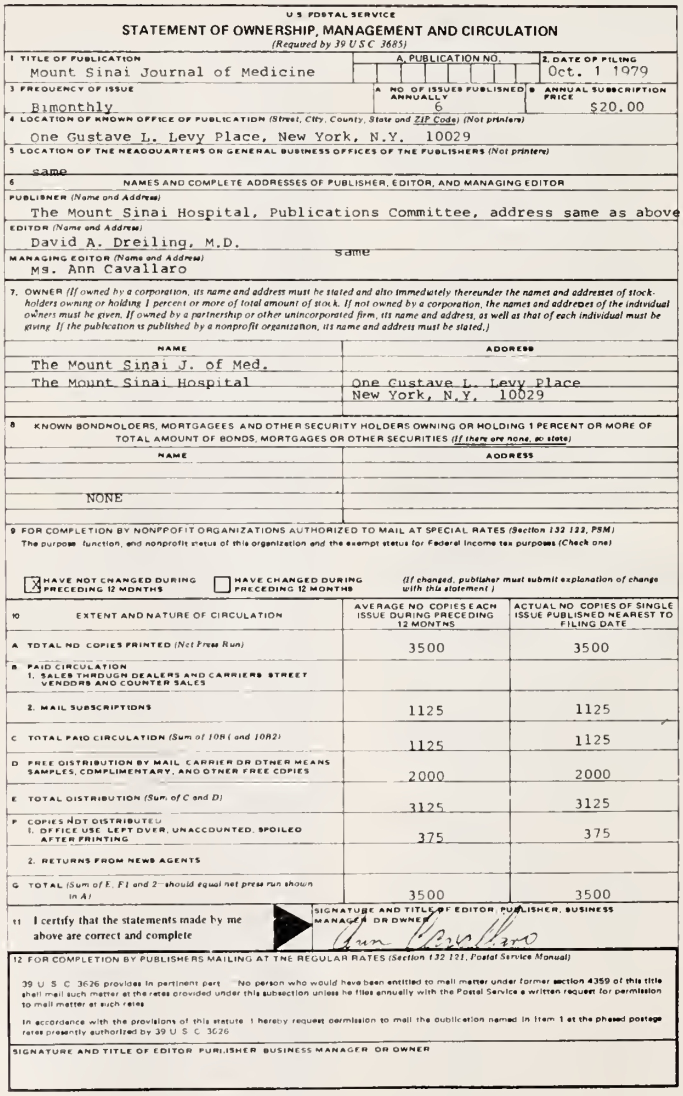

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